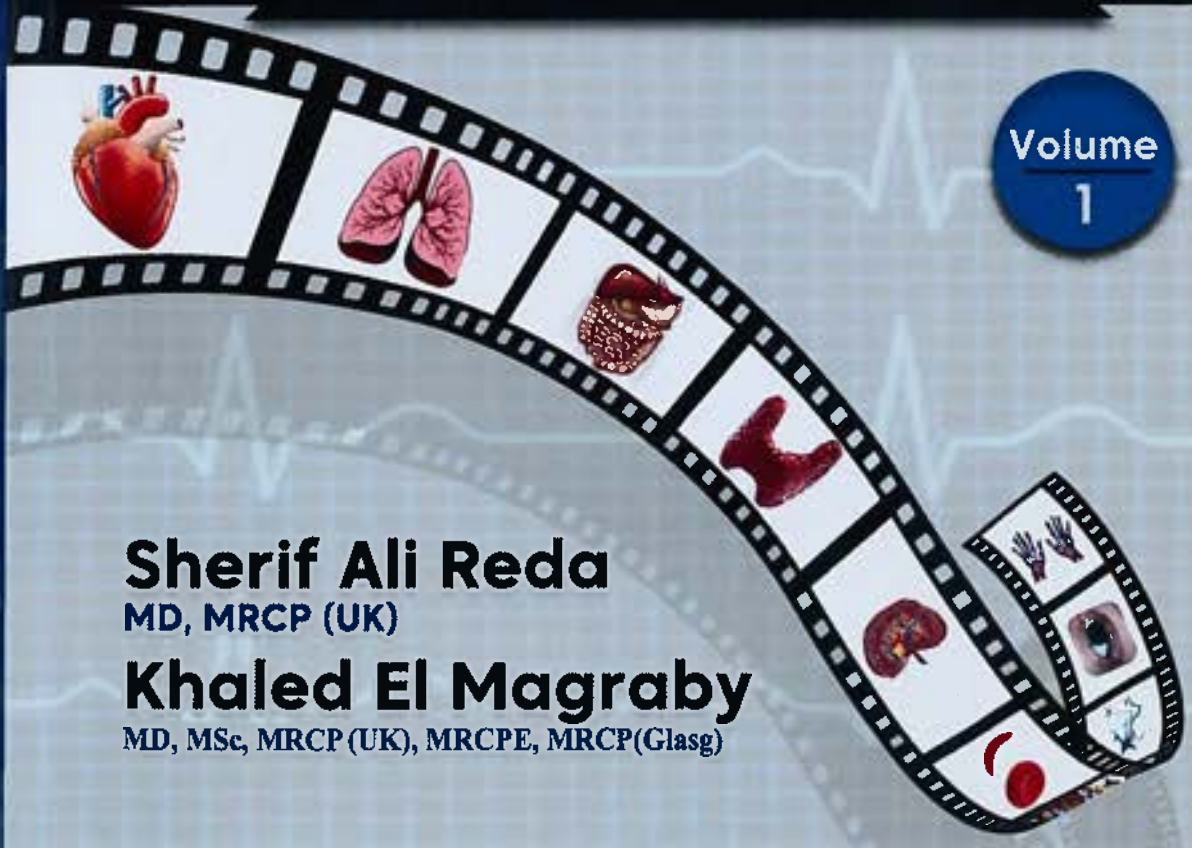
EL MAGRABY & SHERIF'S

3rd Edition

# STEP UP to MRCP

Review Note For Part I & Part II



Volume 1


**Sherif Ali Reda**
MD, MRCP (UK)

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VOLUME 1

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MIDDLE EAST
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publishing and distribution

VOLUME
1

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**ISBN: 978-977- 86708-2-0**
Deposit Number: 11303/2023

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**Publisher**: Middle East & El Marwa for Publishing & Distribution
Cairo, Egypt
Tel. (+20) 1110150022 – (+20) 1211161255
E-mail: ar201078@gmail.com
Publishing Services Manager & Design: Abd El Hamid Abd El Ghafar
Printing Services Manager: Abd El Aleem Adel El Syed
Printed in Egypt

# PREFACE

I feel fortunate and honored to present this third edition of STEP UP TO MRCP to the community of medicine.it has been 7 years since the first edition of this book; the long interval and the increasing demand for new edition of this book- who gained a lot of trust and credibility of the medical society- was the main challenge to publish this edition.

The other challenge was to walk the line between over simplification and data overflow, in the world of internal medicine which is full of guidelines and studies.

this was the main stimulus to fill this book with diagrams, illustrations, photos, radiology material and tables, as to make it easy for everyone to pick up the needed information in an easy way for new and experienced physicians as well.

I would like to thank god for helping me to accomplish this work, and also I would like to thank the god father of this book Khalid Maghraby who invited me to contribute to this edition and helped us during completing this work.

My deepest gratitude goes to my wife Shaimaa and my kids Nada and Mohamed who tolerated me throughout this hard time. to my mother who continued to inspire and pray for me and finally to the soul of my father.

Last but not least, I would like to thank Mr,Abdelhamid the publisher and owner of middle east library ,who spent a lot of time and effort to make this book exists, attractive and in such a wonderful quality.

**S.A. Reda, MD, MRCP (UK)**
June 2023

# FORWARD

Welcome to the world of internal medicine! This medical book is the result of great effort and dedication by its author to provide you with the most updated and comprehensive knowledge of internal medicine.

The book is designed to meet the needs of every medical student, resident, and physician who is pursuing a career in internal medicine. It covers the whole spectrum of internal medicine, from the basics of pathophysiology to the most advanced treatment strategies.

The book is structured in a clear and well-organized manner.

This book is highly recommended for everyone studying internal medicine, particularly those aiming to obtain the MRCP degree. It is an invaluable resource that will help you build a strong foundation in internal medicine and prepare you for success in your medical career.

**Prof. Dr. Khaled Makboul**
Professor of internal medicine and endocrinolgy
Ain Shams University
June 2023

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# Introduction

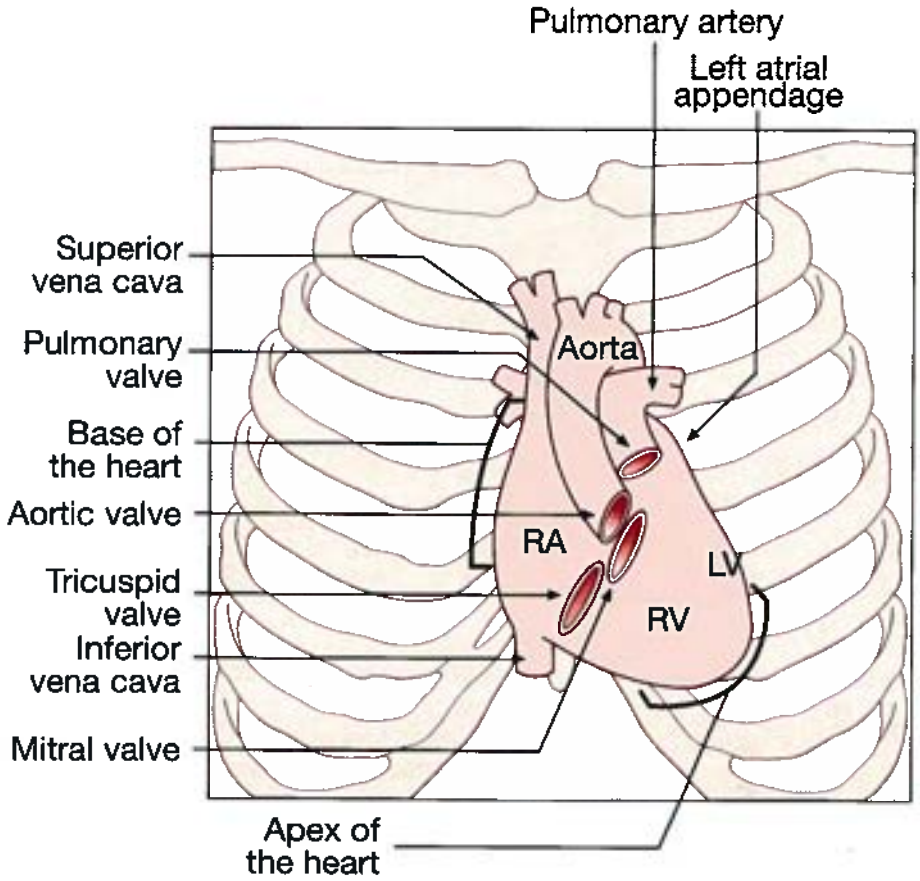
- **Cardiovascular disease is the most frequent cause of adult death in the Western world.**
- **In the UK, one-third of men and one-quarter of women will die as a result of ischemic heart disease.**
- In many developed countries, the incidence of ischemic heart disease has been falling for the last two or three decades, but it is rising in Eastern Europe and Asia.
- Cardiovascular disease will soon become the leading cause of death on all continents.
- Strategies for the treatment and prevention of heart disease can be highly effective and have been subjected to rigorous evaluation.
- The evidence base for the treatment of cardiovascular disease is stronger than for almost any other disease group.
- **Valvular heart disease is common but the etiology varies in different parts of the world.**
- On the **Indian subcontinent and in Africa**, it is predominantly due to **rheumatic fever**, whereas **calcific aortic valve disease is the most common problem in developed countries.**
- Prompt recognition of the development of heart disease is limited by two key factors.
- Firstly, it is often latent; coronary artery disease can proceed to an advanced stage before the patient notices any symptoms.
- Secondly, the diversity of symptoms attributable to heart disease is limited, so different pathologies may frequently present with the same symptoms.

# Anatomy and Physiology of The Heart

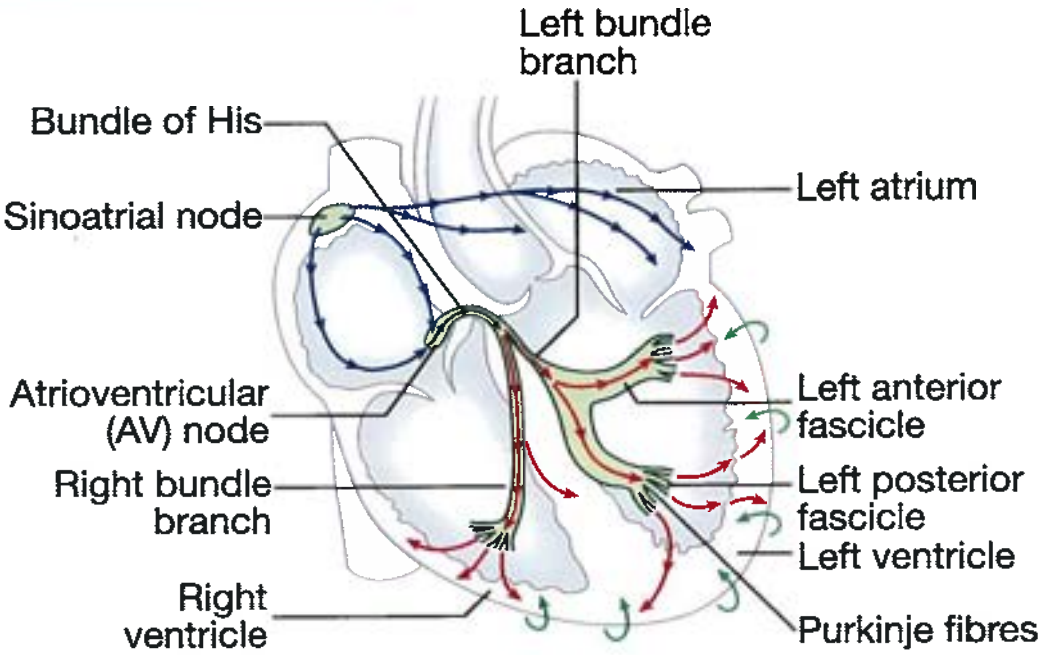
## Anatomy:

**The heart acts as two serial pumps that share several electrical and mechanical components.**

- **The right heart**: circulates blood to the lungs where it is oxygenated.
- **The left heart**: circulates it to the rest of the body.
- **The atria:** are thin-walled structures that act as priming pumps for the ventricles, which provide most of the energy required to maintain the circulation.
- **The atria** are situated posteriorly within the mediastinum where the **left atrium (LA)** sits anterior to the esophagus and descending aorta.
- **The right atrium (RA)** receives blood from the superior and inferior venae cavae and the coronary sinus. The LA receives blood from four pulmonary veins, two from each of the left and right lungs.
- **The ventricles:** are thick-walled structures, adapted to circulating blood through large vascular beds under pressure.
- **The atria and ventricles** are separated by the **annulus fibrosus**, which forms the skeleton for the atrioventricular (AV) valves and electrically insulates the atria from the ventricles.
- **The right ventricle (RV)** is about 2–3 mm thick and triangular in shape. It extends from the annulus fibrosus to near the cardiac apex and sits anterior and to the right of the left ventricle (LV). **The LV** is more conical in shape and in cross-section is nearly circular. It extends from the LA to the apex of the heart.
- **The LV myocardium** is normally around 10 mm thick because it pumps blood at a higher pressure than the RV.
- **Normally, the heart occupies less than 50% of the transthoracic diameter in the frontal plane, as seen on a chest X-ray**. On the patient's left, the cardiac silhouette is formed by the aortic arch, the pulmonary trunk, the left atrial appendage and the LV.
- On the right, the silhouette is formed by the RA and the superior and inferior venae cavae, and the lower right border is formed by the RV In disease states or congenital cardiac abnormalities, the silhouette may change as a result of hypertrophy or dilatation.




Surface anatomy of the heart. The positions of the major cardiac chambers and heart valves are shown. (LV = left ventricle; RA = right atrium; RV = right ventricle)




The cardiac conduction system. Depolarisation starts in the sinoatrial node and spreads through the atria (blue arrows), and then through the atrioventricular node (black arrows). Depolarisation then spreads through the bundle of His and the bundle branches to reach the ventricular muscle (red arrows). Repolarisation spreads from epicardium to endocardium (green arrows).

## Coronary circulation:

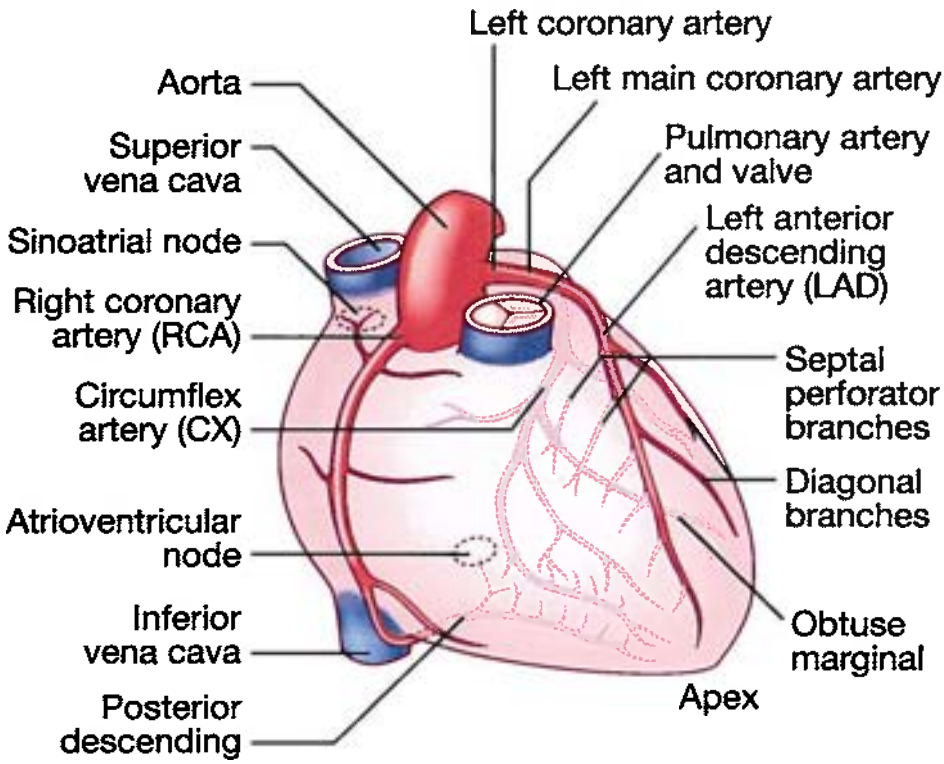
- **the left main and right coronary arteries arise from the left and right sinuses of the aortic root**, distal to the aortic valve Within 2.5 cm of its origin.

### The left main coronary artery:

- divides into the **left anterior descending** artery (LAD), which runs in the anterior interventricular groove,
- the **left circumflex artery** (CX), which runs posteriorly in the atrioventricular groove.
- **The LAD** gives branches to supply the anterior part of the septum (septal perforators) and the anterior, lateral and apical walls of the LV.
- **The CX** gives marginal branches that supply the lateral, posterior and inferior segments of the LV.
- Abrupt occlusion of the LAD or CX causes infarction in the corresponding territory of the LV, **and occlusion of the left main coronary artery is usually fatal.**

**The right coronary artery (RCA):**

- runs in the right atrioventricular groove, giving branches that supply the RA, RV and inferior-posterior aspects of the LV.
- The RCA supplies the sinoatrial (SA) node in about 60% of individuals and the AV node in about 90%. Proximal occlusion of the RCA therefore often results in sinus bradycardia and may also cause AV nodal block.
- Abrupt occlusion of the RCA, to coronary thrombosis, results in infarction of the inferior part of the LV and often the RV.
- **The posterior descending artery**: runs in the posterior interventricular groove and supplies the inferior part of the interventricular septum.
- **This vessel is a branch of the RCA in approximately 90% of people (dominant right system) and is supplied by the CX in the remainder (dominant left system).**




The coronary arteries: anterior view.

# Exercise: physiological changes

## Blood pressure (BP):

- **Systolic increases,**
- **Diastolic remains the same or may decrease slightly with progressive exercise.**
- leads to **increased pulse pressure**
- in healthy young people the increase in MABP is only slight

> ➢ **With heart disease, abnormalities in BP response to exercise are common.**
> ➢ **A fall in BP or failure to rise or excessive rise of SDP >250 mmHg >>> is an indication to terminate the exercise test.**

## Cardiac output (COP):

- ↑ **heart rate** up to 3-fold increase
- ↑ **stroke volume** up to 1.5-fold increase
- ↑ **cardiac output** may be 3-5 fold
- Results from **venous constriction,** vasodilation and increased myocardial contractibility, as well as from the maintenance of right atrial pressure by an **increase in venous return.**

## The compensation mechanisms to sudden hypovolaemia include:

- **Cardiac output (CO) can increase, decrease,** or **stay the same as** (CO = HR × SV). In the clinical scenario of open fracture of the right femur, which is bleeding profusely, it is likely that HR will increase, but **stroke volume may decrease due to the hypovolaemia.**
- **Heart rate (HR) can increase** due to decreased (parasympathetic) vagal stimulation and enhanced sympathetic stimulation with adrenaline.
- **Total peripheral resistance can increase** due to increased sympathetic drive. This causes peripheral vasoconstriction and preserves blood flow to essential organs, such as the brain, heart and kidneys.
- **Venous return increases** if sympathetic output increases, and this is related to the peripheral vasoconstriction. Less blood can pool in the peripheral vessels so it is transported back to the central circulation quickly. This increases venous return and maximises stroke volume.

# Valsalva maneuver

The Valsalva maneuver describes a forced expiration against a closed glottis. This leads to increased intrathoracic pressure which in turn has a number of effects on the cardiovascular system.

## Uses

- to terminate an episode of supraventricular tachycardia
- normalizing middle-ear pressures

## Stages of the Valsalva maneuver

- 1. Increased intrathoracic pressure
- 2. Resultant increase in venous and right atrial pressure reduces venous return
- 3. The reduced preload leads to a fall in the cardiac output (Frank-Starling mechanism)
- 4. When the pressure is released there is a further slight fall in cardiac output due to increased aortic volume
- 5. Return of normal cardiac output

# Cardiovascular pharmacology

## ANTIHYPERTENSIVE MEDICATIONS AT A GLANCE

## Angiotensin-converting enzyme inhibitors (ACEIs)

ACE inhibitors are now the established first-line treatment in **younger** patients with hypertension and are also extensively used to treat **heart failure.**

They are known to be **less** effective in treatment of HTN in **Afro-Caribbean** patients duo to renin activity.

ACE inhibitors are also used to treat **diabetic nephropathy** and have a role in **secondary prevention of ischaemic heart disease.**

### Mechanism of action:

- Inhibit the conversion angiotensin I to angiotensin II
- ACE inhibitors are activated by phase 1 metabolism in the liver

### Side-effects:

- **Cough:** occurs in around **15%** of patients and **may occur up to a year after starting treatment**.
- Thought to be due to increased **bradykinin** levels.
- **Angioedema:** may occur up to a year after starting treatment.
- **Hyperkalaemia:** and better to retest for potassium and creatinine after 10 days from start of treatment if one of them or both increased more than 30% of the base line you have to stop the treatment and use another class of antihypertensive medications.
- **First-dose** hypotension: more common in patients taking diuretics.

### Cautions and contraindications:

- pregnancy and breastfeeding - avoid
- renovascular disease - significant renal impairment may occur in patients who have undiagnosed bilateral renal artery stenosis
- aortic stenosis - may result in hypotension
- hereditary or idiopathic angioedema
- specialist advice should be sought before starting ACE inhibitors in patients with a potassium >= 5.0 mmol/L

### Interactions

- patients receiving high-dose diuretic therapy (more than 80 mg of furosemide a day) - significantly increases the risk of hypotension
  - significantly increases the risk of hypotension

### Monitoring:

- Urea and electrolytes should be checked before treatment is initiated and after increasing the dose
  - A rise in the creatinine and potassium may be expected after starting ACE inhibitors

**Acceptable changes are an increase in serum creatinine, up to 30% from baseline, a decrease in eGFR of up to 25% and an increase in potassium up to 5.5 mmol/l.**

## Angiotensin II receptor blockers

Angiotensin II receptor blockers are generally used in situations where patients have not tolerated an ACE inhibitor, usually due to the development of a cough.

### Examples

- candesartan
- losartan
- irbesartan

Like ACE inhibitors they should be used with caution in patients with renovascular disease. Side-effects include hypotension and hyperkalaemia.

### Mechanism

- **block effects of angiotensin II at the AT1 receptor**

### Evidence base

- shown to reduce progression of renal disease in patients with diabetic nephropathy
- evidence base that losartan reduces CVA and IHD mortality in hypertensive patients

# Beta-blockers

Beta-blockers are an important class of drug used mainly in the management of cardiovascular disorders.

## Indications

- angina
- post-myocardial infarction
- heart failure: beta-blockers were previously avoided in heart failure but there is now strong evidence that certain beta-blockers improve both symptoms and mortality
- arrhythmias: beta-blockers have now replaced digoxin as the rate-control drug of choice in atrial fibrillation
- hypertension: the role of beta-blockers has diminished in recent years due to a lack of evidence in terms of reducing stroke and myocardial infarction.
- thyrotoxicosis
- migraine prophylaxis
- anxiety

## amples

- atenolol
- propranolol: one of the first beta-blockers to be developed. Lipid soluble therefore crosses the blood-brain barrier

## Side-effects

- bronchospasm
- **cold peripheries**
- **fatigue**
- **sleep disturbances, including nightmares**
- erectile dysfunction

## Contraindications

- uncontrolled heart failure
- asthma
- sick sinus syndrome
- **concurrent verapamil use: may precipitate severe bradycardia**

## Hydralazine

Hydralazine is one of the 'older' antihypertensives and is not commonly used nowadays. It is still sometimes used for hypertension in pregnancy , for severe hypertension and with nitrates in treating hypertension with proteinuria in renal impairment.

### Mechanism of action

- **increases cGMP leading to smooth muscle relaxation**

### Contraindications

- systemic lupus erythematous
- ischaemic heart disease/cerebrovascular disease

### Adverse effects

- **tachycardia**
- palpitations
- flushing
- fluid retention
- headache
- **drug-induced lupus**

## Loop diuretics

Furosemide and bumetanide are loop diuretics that act by **inhibiting the Na-K-Cl cotransporter (NKCC) in the thick ascending limb of the loop of Henle, reducing the absorption of NaCl.**
There are two variants of NKCC; loop diuretics act on NKCC2, which is more prevalent in the kidneys.

As loop diuretics work on the apical membrane they must first be filtered into the tubules by the glomerulus before they can have an effect.
Therefore patients with poor renal function may require escalating doses to ensure a sufficient concentration is achieved within the tubules.

### Indications

- heart failure: both acute (usually intravenously) and chronic (usually orally)
- resistant hypertension, particularly in patients with renal impairment

### Adverse effects

- hypotension
- hyponatraemia
- **hypokalaemia, hypomagnesaemia**
- hypochloraemic alkalosis
- **ototoxicity**
- **hypocalcaemia**
- renal impairment (from dehydration + direct toxic effect)
- hyperglycaemia (less common than with thiazides)
- gout

## Thiazide diuretics

Thiazide diuretics work by inhibiting sodium reabsorption at the beginning of the distal convoluted tubule (DCT) by blocking the thiazide-sensitive $Na^+$-$Cl^-$ symporter. Potassium is lost as a result of more sodium reaching the collecting ducts. Thiazide diuretics have a role in the treatment of mild heart failure although loop diuretics are better for reducing overload. The main use of bendroflumethiazide was in the management of hypertension but recent NICE guidelines now recommend other thiazide-like diuretics such as indapamide and chlortalidone.

### Common adverse effects

- dehydration
- postural hypotension
- **hyponatraemia, hypokalaemia, hypercalcaemia***
- **gout**
- **impaired glucose tolerance**
- **impotence**

### Rare adverse effects

- thrombocytopaenia
- agranulocytosis
- photosensitivity rash
- pancreatitis

### Centrally acting antihypertensives:

**Examples of centrally acting antihypertensives include:**

- **Methyldopa**: used in the management of hypertension during pregnancy.

- **Clonidine**: the antihypertensive effect is mediated through stimulating alpha-2 adrenoceptors in the vasomotor centre.
- **Moxonidine (Physiotense ® 0.2 mg tab)**: used in the management of essential hypertension when conventional antihypertensive have failed to control blood pressure.

## Na Nitroprusside

- It is a potent short acting vasodilator, which acts via the nitric oxide pathway to increase **cGMP** within smooth muscle cells.
- It has a rapid hypotensive effect that begins to appear **within 30-60 seconds** of commencing the infusion.
- It is **light sensitive** and degrades to cyanide if exposed to sunlight; as such it is delivered from a covered infusion bag.
- SE: nausea, sweating, headache and twitching.
- Overdose may be associated with accumulation of **cyanide**.
- Cobalamin plays a role in cyanide metabolism and B12 levels tend to fall as cyanide level rise.
- Na nitroprusside use is not recommended in **B12 deficiency** states.
- **Indications:**
  - HTN emergency.
  - Dissecting aortic aneurysm
  - Acute cardiac failure
  - Acute VSD
  - Acute MR
- **Contraindications:**
  - Vit B12 deficiency
  - Severe liver disease
  - Leber's optic atrophy

**EX**: Pt at ICU has severe hypertension on **Na Nitroprusside** and he is stable, after a few hours later he, just after the **nursing shift change**, he has become acutely confused, SOB, central chest pain, abdominal pain, vomiting, BP 100/60 mmHg, PH 7.1, metabolic acidosis, widespread ST depression consistent with myocardial ischaemia >>> **Cyanide poisoning** may be due to uncover of Na Nitroprusside so **it degrades in sunlight to form cyanide** >>>
**Treatment: Dicobalt edetate** 300 mg IV bolus and can be repeated 3 times, **Nitrate** is an alternative potential for cyanide poisoning if edetate is unavailable.

## New drugs

### Direct renin inhibitors:

- e.g. **Aliskiren** (branded as Rasilez).
- By inhibiting renin blocks the conversion of angiotensinogen to angiotensin I.
- No trials have looked at mortality data yet. Trials have only investigated fall in blood pressure. Initial trials suggest aliskiren reduces BP to a similar extent as ACEIs or ARBs.
- Adverse effects were uncommon in trials although diarrhoea was occasionally seen.
- Only current role would seem to be in patients who are intolerant of more established antihypertensive drugs.

### 4TH generation of calcium channel blockers

## Nitrates: BNF 80 (2021)

**CONTRA-INDICATIONS** Aortic stenosis. cardiac tamponade.

- Constrictive pericarditis.
- hypertrophic cardiomyopathy.
- hypotensive conditions.
- hypovolemia. marked anemia.
- mitral stenosis. raised intracranial pressure due to cerebral hemorrhage.
- raised intracranial pressure due to head trauma.
- toxic pulmonary oedema
- CAUTIONS Heart failure due to obstruction.
- hypothermia.
- hypothyroidism.
- hypoxemia.
- malnutrition.
- metalcontaining transdermal systems should be removed before magnetic resonance imaging procedures, cardioversion, or diathermy.
- recent history of myocardial infarction.
- susceptibility to angle-closure glaucoma.
- tolerance.
- ventilation and perfusion abnormalities

**Tolerance** Many patients on long-acting or transdermal nitrates
Rapidly develop tolerance (with reduced therapeutic effects).
Reduction of blood-nitrate concentrations to low levels for 4 to 12 hours each day usually maintains effectiveness in such patients.

- If tolerance is suspected during the use of transdermal patches they should be left off for 8–12 hours (usually overnight) in each 24 hours;

- in the case of modifiedrelease tablets of isosorbide dinitrate (and conventional BNF 80 Acute coronary syndromes 231 Cardiovascular system 2 www.webofpharma.com formulations of isosorbide mononitrate),
- the second of the two daily doses should be given after about 8 hours rather than after 12 hours.
- Conventional formulations of isosorbide mononitrate should not usually be given more than twice daily unless small doses are used;
- modifiedrelease formulations of isosorbide mononitrate should only be given once daily, and used in this way do not produce tolerance.
- **Elderly Prescription potentially inappropriate (STOPP criteria)** if prescribed a long-acting nitrate with persistent postural hypotension i.e.,
- recurrent drop in systolic blood pressure 20 mmHg (risk of syncope and falls).

## Ivabradine (Procoralan ®):

- A new class of anti-anginal drug which works by reducing the heart rate.
- It acts on **the If ('funny') ion current** which is highly expressed in the sinoatrial node **(SAN),** reducing cardiac pacemaker activity.

### Adverse effects:

- **visual effects**, particular **luminous phenomena**, are common.
- **Bradycardia,** heart block.
- headache
- There is no evidence currently of superiority over existing treatments of stable angina.

**NB**: Pt. with IHD with angina attacks: **ASA** + **Statin** + **Atenolol** 100 md OD + **Nifedipine** MR 30mg OD ± **Isosorbide mononitrate** is 10mg bid ± **Ivabradine** ± **Nicorandil**.

**NB**: EX: Pt. with **Prinz metal's angina** treatment = **dihydropyridine** calcium channel blocker e.g., **Felodipine.**

**Non-atherosclerotic angina** would be associated with conditions such as

- Anaemia
- Thyrotoxicosis
- Aortic stenosis
- Aortic regurgitation
- HOCM

# Adenosine

The effects of adenosine are enhanced by dipyridamole (anti-platelet agent) and blocked by theophyllines.

**ADenosine:**
- **Dipyridamole enhances** effect.
- **Aminophylline reduces** effect.

## Mechanism of action:

- causes transient **heart block** in the AV node
- **agonist of the A1 receptor in the atrioventricular node,** which inhibits adenylyl cyclase thus reducing cAMP and causing hyperpolarization by increasing outward potassium flux
- adenosine has a very short half-life of about 8-10 seconds

It should be given as the first line **for any narrow complex tachycardia with stable haemodynamic.**

It can be used in **broad complex tachycardia if** you are not sure is it supraventricular or a ventricular tachycardia, so consider adenosine to differentiate between **SVT with aberrant conduction** and **VT.**

## Adverse effects:

- **chest pain**
- **bronchospasm**
- transient flushing
- can enhance conduction down accessory pathways, resulting in increased ventricular rate (e.g. WPW syndrome)

# Amiodarone (Cordarone®)

Amiodarone is a **class III antiarrhythmic agent** used in the treatment of atrial, nodal and ventricular tachycardias.

The main mechanism of action is by **blocking potassium channels** which inhibits repolarisation and hence prolongs the action potential.

It also has other actions such as **blocking sodium channels** (a class Ia effect).

Amiodarone is considered as **both** class **Ia** and class **III.**

**The use of amiodarone is limited by a number of factors:**

- **Long half-life (20-100 days).**
- Should ideally be given into central veins (causes **thrombophlebitis**).
- Has **proarrhythmic** effects due to **lengthening of the QT interval**.
- **Interacts** with drugs commonly used concurrently e.g., decreases metabolism of warfarin (**P450 inhibitor**), so increase risk of bleeding.
- Numerous long-term adverse effects (see below).

**Monitoring of patients taking amiodarone:**

- TFT, LFT, U&E, CXR **prior** to treatment.
- TFT, LFT every 6 months.

## Adverse effects of amiodarone use:

- Thyroid dysfunction: (Hypothyroidism in 30% and thyrotoxicosis in 15%)
- **Corneal deposits**: in at least **90%** of cases.
- Pulmonary **fibrosis**/pneumonitis (in 5%)
- Liver fibrosis/hepatitis (less than 5%)
- Peripheral neuropathy, myopathy
- Photosensitivity rash (rash on the forearms and face)
- **'Slate-grey' appearance**
- Thrombophlebitis and injection site reactions
- Bradycardia
- lengths QT interval

**NB:** All antiarrhythmic drugs have the potential to cause arrhythmias. Coexistent **hypokalaemia** significantly increases this risk.

So should checking the urea and electrolytes prior to commencing a patient on amiodarone.

**NB**: **Amiodarone toxicity** occurs in approximately **5%** of patients. This can vary from **acute respiratory distress** to a picture of **cough, pleuritic chest pain**, pulmonary **infiltrates** and small **pleural effusions** to **interstitial pneumonitis** and eventually **progressive pulmonary fibrosis**.

Due to it **long half-life,** amiodarone toxicity takes some **weeks to resolve; as such corticosteroids** are added when therapy is discontinued as this may lead to more rapid resolution of symptoms.

# Amiodarone and the thyroid gland

**Around 1 in 6** patients taking amiodarone develop thyroid dysfunction.

The incidence of amiodarone induced thyroid dysfunction has **no** relationship at all to photosensitivity.

**Bizarre thyroid function tests (TFTs) seem to feature at the MRCP exam and amiodarone is usually the cause.**

Amiodarone contains **75 mg of iodine** per 200 mg tablet.

In addition, the **half-life is very long (100 days)** and can result in prolonged effects even after stopping therapy for several months.

## Amiodarone-induced hypothyroidism (AIH):

The pathophysiology of amiodarone-induced hypothyroidism (AIH) is thought to be due to the high iodine content of amiodarone causing a **Wolff-Chaikoff effect** (it is an auto regulatory phenomenon where thyroxine formation is inhibited due to high levels of circulating iodide). **Iodine driven inhibition of thyroid hormone synthesis.**

**Amiodarone may be continued** if this is desirable especially in cases of VT it would be unwise to withdraw amiodarone abruptly. So **continue amiodarone and add thyroxine.**

The **typical results** of amiodarone-induced hypothyroidism which inhibits the peripheral conversion of T4 to T3 is >>>>

↑**TSH**, **low T3** and **normal or elevated T4**.

As T3 is the most active thyroid hormone, the low T3 feedbacks at the pituitary level result in increased TSH secretion.

## Amiodarone-induced thyrotoxicosis (AIT):

Amiodarone-induced thyrotoxicosis (AIT) may be divided into two types:

| | AIT type 1 | AIT type 2 |
|---|---|---|
| **Pathophysiology** | Accelerated thyroid hormone synthesis secondary to **iodide load**. (**Jod-Basedow effect**).<br><br>Occurs in patients **with** underlying latent thyroid pathology. | Amiodarone-related **destructive thyroiditis** with direct effect of amiodarone on the follicular cells, with breakdown of cells and therefore **release of preformed** thyroid hormones T4 and T3.<br><br>This is a **direct** toxic effect of amiodarone on the thyroid follicular cells, and occurs in patients **without** underlying thyroid disease.<br><br>Clinically **neck tenderness**. |
| **Goitre** | **Present** | Absent |
| **Duplex US on thyroid for blood flow** (is the most useful to differentiate between both types) ☺ | **Increase** | Decrease |
| **Iodine-131 uptake scan** | **Normal or high** | Low or none |
| **Thyroid autoantibodies** | **Positive** | |
| **IL-6** | | **High IL-6** |
| **Management** | **Carbimazole** 40 mg OD or<br>**K perchlorate** or **lithium carbonate** or **Surgery** | Corticosteroids (**prednisolone 40 mg/d**) |

Unlike in AIH, **amiodarone should be stopped** if possible in patients who develop **AIT**.

And if necessary **other anti-arrhythmic** could be used to maintain sinus rhythm such as sotalol or flecainide (if not contraindicated).

**If** amiodarone cannot be withdrawn then **total thyroidectomy** should be considered.

## Flecainide

Flecainide is a Vaughan Williams class **1c** antiarrhythmic.

It slows conduction of the action potential by acting as a potent **sodium channel blocker.**

This may be reflected by **widening of the QRS complex** and **prolongation of the PR interval.**

### Indications:

- **Atrial fibrillation.**
- SVT associated with accessory pathway e.g. **WPW syndrome.**

### Adverse effects:

- Negatively inotropic
- Bradycardia
- Proarrhythmic
- Visual disturbances
- Oral paraesthesia

### Contraindicated:

- **Structural** heart disease.
- **Ischemic** heart disease

# Warfarin

Warfarin is an oral anticoagulant that was used first-line for many years in both the management of venous thromboembolism and reducing stroke risk in patients with atrial fibrillation. It has now been largely superseded by the use of direct oral anticoagulants (DOACs) which do not require the same level of monitoring as warfarin.

## Mechanism of action

- inhibits epoxide reductase preventing the reduction of vitamin K to its active hydroquinone form
- this in turn acts as a cofactor in the carboxylation of clotting **factor II, VII, IX and X (mnemonic = 1972)** and protein C.

## Indications

- mechanical heart valves
  - target INR depends on the valve type and location
  - mitral valves generally require a higher INR than aortic valves.
- second-line after DOACs:
  - venous thromboembolism: target INR = 2.5, if recurrent 3.5
  - atrial fibrillation, target INR = 2.5

## Monitoring

- patients are monitored using the INR (international normalised ratio), the ratio of the prothrombin time for the patient over the normal prothrombin time.
- warfarin has a long half-life and achieving a stable INR may take several days
- there are a variety of loading regimes and computer software is now often used to alter the dose

## Factors that may potentiate warfarin

- liver disease
- P450 enzyme inhibitors, e.g.: amiodarone, ciprofloxacin
- cranberry juice
- drugs which displace warfarin from plasma albumin, e.g. NSAIDs
- inhibit platelet function: NSAIDs

## Side-effects

- haemorrhage
- teratogenic, although **can be used in breastfeeding mothers**
- skin necrosis

  - when warfarin is first started biosynthesis of protein C is reduced
  - this results in a temporary procoagulant state after initially starting warfarin, normally avoided by concurrent heparin administration
  - thrombosis may occur in venules leading to skin necrosis
- purple toes

Warfarin should be **taken** about **the same time each day**, if the patient forgot to take her warfarin last day, **she should take it later that day**, and she should **not take a double dose the next day**. She should make a note and let the anticoagulation clinic know when she attends.

## Management of high INR

The following is based on the BNF guidelines, which in turn take into account the British Committee for Standards in Haematology (BCSH) guidelines.

| Situation | Management |
|---|---|
| **Major bleeding** | Stop warfarin<br>Give intravenous vitamin K 5mg<br>Prothrombin complex concentrate - if not available then FFP* |
| **INR > 8.0**<br>**Minor bleeding** | Stop warfarin<br>Give intravenous vitamin K 1-3mg<br>Repeat dose of vitamin K if INR still too high after 24 hours<br>Restart warfarin when INR < 5.0 |
| **INR > 8.0**<br>**No bleeding** | Stop warfarin<br>Give vitamin K 1-5mg by mouth, using the intravenous preparation orally<br>Repeat dose of vitamin K if INR still too high after 24 hours<br>Restart when INR < 5.0 |
| **INR 5.0-8.0**<br>**Minor bleeding** | Stop warfarin<br>Give intravenous vitamin K 1-3mg<br>Restart when INR < 5.0 |
| **INR 5.0-8.0**<br>**No bleeding** | Withhold 1 or 2 doses of warfarin<br>Reduce subsequent maintenance dose |

as FFP can take time to defrost prothrombin complex concentrate should be considered in cases of intracranial haemorrhage

# Adenosine diphosphate (ADP) receptor inhibitors

## Examples include:

- Clopidogrel
- Prasugrel
- Ticagrelor
- Ticlopidine

## Mechanism of ADP receptor inhibitors

- Adenosine diphosphate (ADP) is one of the main platelet activation factors, mediated by G-coupled receptors P2Y1 and P2Y12.
- The main target of ADP receptor inhibition is the P2Y12 receptor, as it is the one which leads to sustained platelet aggregation and stabilisation of the platelet plaque.

## Evidence

- As aspirin and ADP inhibitors work by blocking different platelet aggregation pathways, their potential synergy has been studied by multiple clinical trials, particularly in high-risk patients presenting with acute coronary syndrome (ACS) or undergoing percutaneous coronary intervention (PCI).
- Clopidogrel used to be the most commonly used ADP inhibitor, however, due to its interindividual variability in antiplatelet effects, newer agents such as prasugrel and ticagrelor have been developed.
- Multiple trials since have shown a marked reduction in short- and long-term ischaemic events when using prasugrel and aspirin, compared to clopidogrel and aspirin in moderate- to high-risk ACS patients.[1]
- Current NICE guidelines for ACS, therefore, recommend starting dual antiplatelet treatment (DAPT) with Aspirin (75mg daily) and Ticagrelor (90mg twice daily) for 12 months, as a secondary prevention strategy.
- NICE guidelines for people with ACS undergoing PCI recommend aspirin (75-100mg daily) in combination with either prasugrel (10mg daily), ticagrelor (90mg twice daily), or clopidogrel (75mg daily, if prasugrel or ticagrelor are not suitable) for 12 months, with aspirin alone thereafter.[2]

## Notable adverse effects

- ticagrelor may cause dyspnoea
  - **due to the impaired clearance of adenosine**

## Interactions and contraindications

- A drug interaction exists between clopidogrel and proton pump inhibitors, particularly omeprazole and esomeprazole, leading to reducing antiplatelet effects.
- Patients with prior stroke or transient ischaemic attack, high risk of bleeding, and prasugrel hypersensitivity are absolute contraindications to prasugrel use.
- Ticagrelor is contraindicated in patients with a high risk of bleeding, those with a history of intracranial haemorrhage, and those with severe hepatic dysfunction. It is also to be used with caution in those with acute asthma or COPD, as ticagrelor-treated patients experience higher rates of dyspnoea.

- **NB**: **TTP** (thrombotic thrombocytopenic purpura) can occur in **less than 1%** of patients receiving **clopidogril** or ticlopidine >>> **peripheral blood film** >>> **fragmented RBCs.**
- **EX**: Pt after **2 weeks** from PCI and Plavix usage, develop Rt. sided weakness, bleeding tendency, low platelets, anaemia, renal impairment, fever, Disturbed LOC with confusion >>> **TTP due to clopidogril**.

# Glycoprotein IIb/IIIa receptor antagonists

## Examples include;

- abciximab
- eptifibatide
- tirofiban

# Dabigatran

Dabigatran is an oral anticoagulant that works by being a **direct thrombin inhibitor.** It is one of the drugs developed over the past 20 years as an alternative to warfarin, with the advantage that it does not require regular monitoring.

## Dabigatran is currently used for two main indications.

**Firstly** it is an option in the prophylaxis of venous thromboembolism following hip or knee replacement surgery.
**Secondly,** it is also licensed in the UK for prevention of stroke in patients with non-valvular atrial fibrillation who have one or more of the following risk factors present:

- previous stroke, transient ischaemic attack or systemic embolism
- left ventricular ejection fraction below 40%

- symptomatic heart failure of New York Heart Association (NYHA) class 2 or above
- age 75 years or older
- age 65 years or older with one of the following: diabetes mellitus, coronary artery disease or hypertension

**the known side-effects** Unsurprisingly haemorrhage is the major adverse effect.
Doses should be reduced in chronic kidney disease and dabigatran should not be prescribed if the creatinine clearance is < 30 ml/min.

## Reversing the effects

Idarucizumab cab be used for rapid reversal of the anticoagulant effects of dabigatran.

## Drug Safety Update

The RE-ALIGN study showed significantly higher bleeding and thrombotic events in patients with recent mechanical heart valve replacement using dabigatran compared with warfarin.

Previously there had been no guidance to support the use of dabigatran in patients with prosthetic heart valves but the advice has now changed to dabigatran being contraindicated in such patients.

It is oral anticoagulant, **anti- thrombin** (factor **2**)

The drug dabigatran has a **half-life elimination of 12-14 hours** in normal subjects; it lasts **longer** in patients with abnormal **kidney** function.

Dabigatran **should be stopped before colonoscopy**:-
For patients with **normal** creatinine clearance, it is safe to **discontinue the drug 1 to 2 days before colonoscopy procedure**.

For the patient with **CKD**, it is better **to stop the drug 3 to 5 days before the procedure**. An even longer period might be considered for those undergoing major surgery, spinal puncture or placement of epidural catheter (in whom complete haemostasis is warranted).

The drug contributes to INR elevation but its effect cannot be monitored in such manner. Similarly, use of **aPTT** can only provide an approximation of **dabigatran's anticoagulant activity**. **Haemodialysis** removes around **60%** of the drug over 2 to 3 hours

# Combination antiplatelet and anticoagulant therapy

With the increase in comorbidity, it is now common to find that a patient has an indication for both an antiplatelet (e.g. established cardiovascular disease) and an anticoagulant (e.g. atrial fibrillation, venous thromboembolism or valvular heart disease).
However, combination therapy increases the risk of bleeding and may not be needed in all cases.

**How should this be managed?**

Whilst there are not guidelines to cover every scenario a recent review in the BMJ offered an expert opinion outlining the approach in common scenarios.

## Secondary prevention of stable cardiovascular disease with an indication for an anticoagulant

- normally in this situation, all patients are recommended to be prescribed an antiplatelet
- if an indication for anticoagulant exists (for example atrial fibrillation) it is indicated that **anticoagulant monotherapy is given without the addition of antiplatelets**

## Post-acute coronary syndrome/percutaneous coronary intervention

- in these patients, there is a much stronger indication for antiplatelet therapy
- generally patients are given triple therapy **(2 antiplatelets + 1 anticoagulant)** for 4 weeks-6 months after the event and dual therapy (1 antiplatelet + 1 anticoagulant) to complete 12 months
- there is variation from patient to patient however given that the stroke risk in atrial fibrillation varies according to risk factors.

## Venous thromboembolism (VTE)

- if a patient on antiplatelets develops a VTE they are likely to be prescribed anticoagulants for 3-6 months
- a HAS-BLED score should be calculated. Those with a low risk of bleeding may continue antiplatelets. In patients with an intermediate or high risk of bleeding consideration should be given to stopping the antiplatelets

For more information please see BMJ 2017;358:j3782

## Parenteral anticoagulation

Parenteral anticoagulants are used for the prevention of venous thromboembolism and in the management of acute coronary syndrome.
**Unfractionated heparin**
**low molecular weight heparin**

### Fondaparinux

Activates antithrombin III, which in turn potentiates the inhibition of coagulation factors Xa. It is given subcutaneously.

### Direct thrombin inhibitors

Examples include bivalirudin. These are generally given intravenously. Dabigatran is a type of direct thrombin inhibitor that is taken orally. It is often grouped alongside the direct oral anticoagulants (DOACs).

## Antiplatelets: summary of latest giudlines

The table below summarizes the most recent guidelines regarding antiplatelets:

| Diagnosis | 1st line | 2nd line |
|---|---|---|
| **Acute coronary syndrome (medically treated)** | **Aspirin (lifelong) & ticagrelor (12 months)** | If aspirin contraindicated, clopidogrel (lifelong) |
| **Percutaneous coronary intervention** | **Aspirin (lifelong) & prasurgrel or ticagrelor (12 months)** | If aspirin contraindicated, clopidogrel (lifelong) |
| **TIA** | **Clopidogrel (lifelong)** | **Aspirin (lifelong) & dipyridamole (lifelong)** |
| **Ischaemic stroke** | **Clopidogrel (lifelong)** | **Aspirin (lifelong) & dipyridamole (lifelong)** |
| **Peripheral arterial disease** | **Clopidogrel (lifelong)** | **Asprin (lifelong)** |

# Statins

**Statins inhibit the action of HMG-CoA reductase, the rate-limiting enzyme in hepatic cholesterol synthesis.**

## Adverse effects

myopathy: includes myalgia, myositis, rhabdomyolysis and asymptomatic raised creatine kinase. Risks factors for myopathy include advanced age, female sex, low body mass index and presence of multisystem disease such as diabetes mellitus. Myopathy is more common in lipophilic statins (simvastatin, atorvastatin) than relatively hydrophilic statins (rosuvastatin, pravastatin, fluvastatin)

- liver impairment: the 2014 NICE guidelines recommend checking LFTs at baseline, 3 months and 12 months. Treatment should be discontinued if serum transaminase concentrations rise to and persist at 3 times the upper limit of the reference range
- there is some evidence that statins may increase the risk of intracerebral haemorrhage in patients who've previously had a stroke. This effect is not seen in primary prevention. For this reason the Royal College of Physicians recommend avoiding statins in patients with a history of intracerebral haemorrhage

## Contraindications

- **macrolides (e.g. erythromycin, clarithromycin) are an important interaction**. Statins should be stopped until patients complete the course
- **pregnancy**

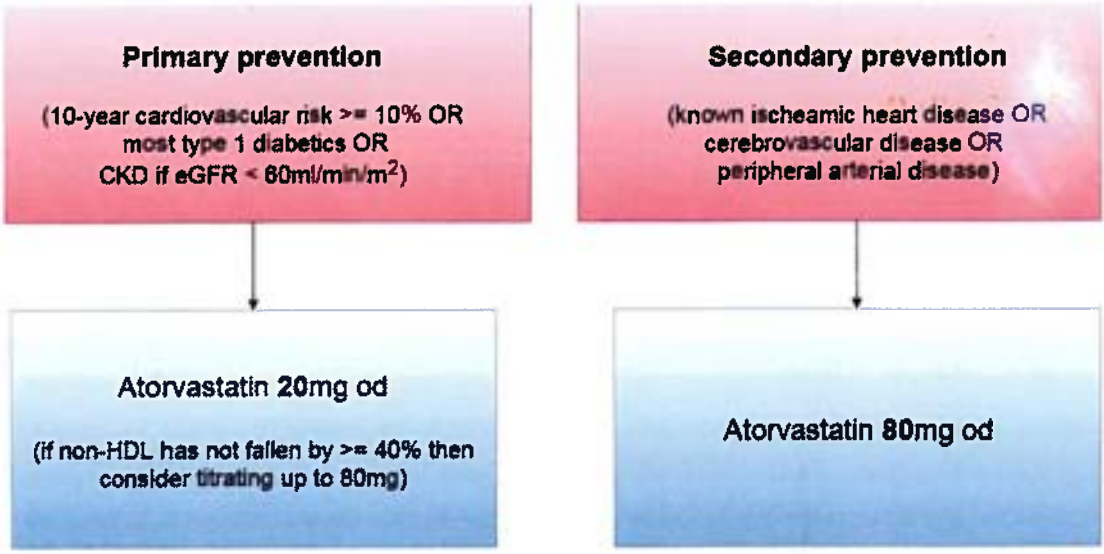
## Who should receive a statin?

- all people with established cardiovascular disease (stroke, TIA, ischaemic heart disease, peripheral arterial disease)
- following the update, NICE recommend anyone with a 10-year cardiovascular risk >= 10%
- patients with type 2 diabetes mellitus should now be assessed using QRISK2 like other patients are, to determine whether they should be started on statins
- patients with type 1 diabetes mellitus who were diagnosed more than 10 years ago OR are aged over 40 OR have established nephropathy

Statins should be taken at night as this is when the majority of cholesterol synthesis takes place. This is especially true for simvastatin which has a shorter half-life than other statins.

NICE currently recommends the following for the prevention of cardiovascular disease:

- atorvastatin 20mg for primary prevention
  - increase the dose if non-HDL has not reduced for >= 40%
- atorvastatin 80mg for secondary prevention




## Nicorandil

Nicorandil is a vasodilatory drug used to treat angina. It is **a potassium-channel** activator with vasodilation is through activation of guanylyl cyclase which results in increase cGMP.

### Adverse effects

- **headache**
- **flushing**
- skin, mucosal and eye ulceration
  - **gastrointestinal ulcers** including **anal ulceration**

### Contraindications

- left ventricular failure

# Digoxin and digoxin toxicity

Digoxin is a cardiac glycoside now mainly used for rate control in the management of atrial fibrillation.

As it has positive inotropic properties it is sometimes used for **improving symptoms (but not mortality)** in patients with heart failure.

## Mechanism of action:

- Decreases conduction through the AVN which slows the ventricular rate in atrial fibrillation and flutter.
- Stimulates vagus nerve.
- Increases the force of cardiac muscle contraction due to **inhibition of the $Na^+/K^+$ ATPase pump**.

Digoxin follows first order kinetics and has a **half-life of 1.6 days** in a patient with normal renal function.

65% of the drug absorbed remains in the system after one day.

Subsequent doses **gradually accumulate** until a **steady state concentration** is achieved after **4 to 5 days**.

Digoxin is concentrated in **tissues** and therefore **has a large apparent volume of distribution.**

Serum digoxin concentrations are **not** significantly altered by large changes in fat tissue weight so that its **distribution space correlates best with lean (that is, ideal) body weight, not total body weight.**

**Approximately 25% of digoxin in the plasma is bound to protein.**

**N.B:** The **half-life** of digoxin is around **36-48 hours**. This results in **a delay** before steady plasma levels are seen, so that **the full effect will not be seen for one week. So the full effect of this treatment would not be apparent for at least a week due to long half-life.**

## Digoxin toxicity:

**Plasma concentration alone does not determine** whether a patient has developed digoxin toxicity. The BNF advises that the likelihood of toxicity increases progressively from 1.5 to 3 mcg/l.

## Features:

- Generally unwell, lethargy, nausea & vomiting, anorexia, confusion, yellow-green vision
- ECG features:
  - **Down-sloping ST depression ('reverse tick')**
  - **Flattened/inverted T waves**
  - **Arrhythmias (e.g. AV block, bradycardia, PVC)**
  - **Prolonged PR interval**
  - **Short QT interval**

## Precipitating factors:

- Classically: **hypokalaemia** (although hyperkalaemia may also worsen digoxin toxicity, although this is very small print).
- Increasing age
- Renal failure
- Myocardial ischaemia
- Acidosis (**Hypo PH**).
- **Hypo**magnesaemia,
- **Hypo**albuminaemia
- **Hypo**thermia
- **Hypo**thyroidism
- **Hypercalcaemia**, **Hypernatremia**
- Drugs: **amiodarone,** quinidine, verapamil, diltiazem, spironolactone (competes for secretion in distal convoluted tubule therefore reduce excretion), cyclosporine.
- Also drugs which cause hypokalaemia e.g.,thiazides and loop diuretics.

**ALL HYPO**

Except

HYPER **CA** & HYPER **Na**

## Management:

- Digi bind IV **(Digoxin specific Fab Fragment)( Digibind)**
- Correct arrhythmias (atropine IV in bradycardia)
- In absence of digoxin specific antibodies, insertion of a temporary pacing wire may improve the heart rate.
- Monitor K+
- If early ingestion >>> NGT and 75 gm charcoal

**Indications** for administration of **Digoxin specific Fab Fragment**:

1) Haemodynamically instability.
2) Life threatening arrhythmias: persistent **bradycardia** in spite of atropine or **Tachyarrhythmia** (especially ventricular).
3) Ingestion of > 10 mg digoxin in adults and 4 mg in children.
4) Plasma digoxin level > 13 nmol/L
5) Serum K > 5 mmol/L in acute toxicity.

**NB:** If patient has ventricular tachycardia (VT) secondary to digoxin toxicity and is unstable haemodynamically. In the setting of digoxin toxicity DC cardioversion is not used unless all other measures have been exhausted because it is usually unsuccessful. The most usefful drugs in this seting are lidocaine and phenytoin. Amiodarone and procainamide may increase digoxin levels and
should be avoided.

**Digoxin toxicity** with **haemodynamically unstable VT** >>>> the most appropriate **first** treatment is **Phenytoin 250 mg IV over 5 min, (NOT DC Cardioversion).**

**If** this Phenytoin is not effective, so **Lidocaine IV** may be used as next drug therapy.

**EX**: Patient with **Rheumatoid Arthritis** and **echo** finding of **speckled myocardium** which make the **amyloidosis** is the most likely underlying cause.

**Digoxin is contraindicated in amyloid patients** as patients are extremely sensitive to it. This is possible due to digoxin binding in the amyloid fibrils.

# Clinical Cardiology

## Heart sounds

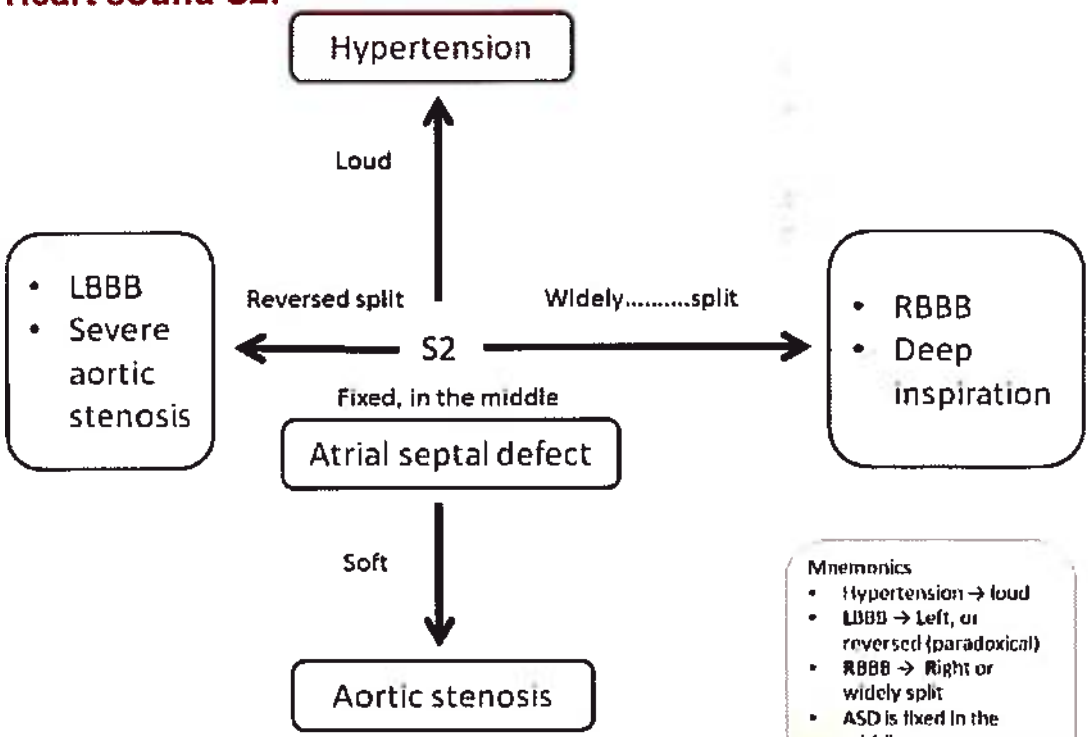
The first heart sound (S1) is caused by closure of the mitral and tricuspid valves whilst the second heart sound (S2) is due to aortic and pulmonary valve closure

### Heart sound S1:

- closure of mitral and tricuspid valves
- loud in mitral stenosis
- soft if long PR or mitral regurgitation

**NB: closure of mitral valve** >>> corresponds with **QRS complex** in ECG.

### Heart sound S2:




S2 is caused by the closure of the aortic valve (A2) closely followed by that of the pulmonary valve (P2)

## Causes of a loud S2:

- **Hypertension**: **systemic** (loud A2) or **pulmonary** (loud P2)
- **Hyperdynamic states**
- **Atrial septal defect** without **pulmonary hypertension**

## Causes of a soft S2

- **AS**

## Causes of fixed split S2

- **ASD**

## Causes of a widely split S2

- **RBBB**
- Deep inspiration
- Pulmonary stenosis
- Severe mitral regurgitation

## Causes of a reversed (paradoxical) split S2 (P2 occurs before A2)

- **LBBB**
- **Severe aortic stenosis**
- Right ventricular pacing
- WPW type B (causes early P2)
- Patent ductus arteriosus

**Second heart sound (S2)**

- Loud: hypertension
- Soft: AS
- Fixed split: ASD
- Reversed split: LBBB

## S3 (third heart sound):

- Caused by **diastolic filling of the ventricle.**
- **Considered normal if < 30 years old (may persist in women up to 50 years old).**
- Heard in:
  - **left ventricular failure (e.g. dilated cardiomyopathy)** and
  - **Constrictive pericarditis (called a pericardial knock).**
- **NB: Gallop rhythm (S3) is an early sign of LVF.**

## S4 (fourth heart sound):

- Caused by atrial contraction against a stiff ventricle.
- May be heard in **aortic stenosis**, HOCM, hypertension.
- In HOCM a double apical impulse may be felt as a result of a palpable S4.

# Murmurs

## Ejection systolic:

- **louder on expiration**
  - Aortic stenosis (ejection systolic murmur radiating to the carotid area).
  - HOCM.
- **louder on inspiration**
  - Pulmonary stenosis,
  - ASD. Fallot's (as only P2).
  - Fallot's (as only P2).

## Holosystolic (pansystolic):

- **Mitral / Tricuspid regurgitation** (high-pitched and 'blowing' in character).
  - **tricuspid regurgitation becomes louder during inspiration, unlike mitral stenosis**
  - during inspiration, the venous blood flow into the right atrium and ventricle are increased → increases the stroke volume of the right ventricle during systole
- **VSD ('harsh' in character).**

**If small VSD >>> systolic murmur at Left Sternal Edge (LSE)**

## Late systolic:

- Mitral valve prolapse
- Coarctation of aorta

## Early diastolic:

- **Aortic regurgitation** (high-pitched and 'blowing' in character)
- Graham-Steel murmur (pulmonary regurgitation, again high-pitched and 'blowing' in character)

## Mid-late diastolic:

- **Mitral stenosis** ('rumbling' in character)
- **Austin-Flint murmur** (severe aortic regurgitation, again is 'rumbling' in character)

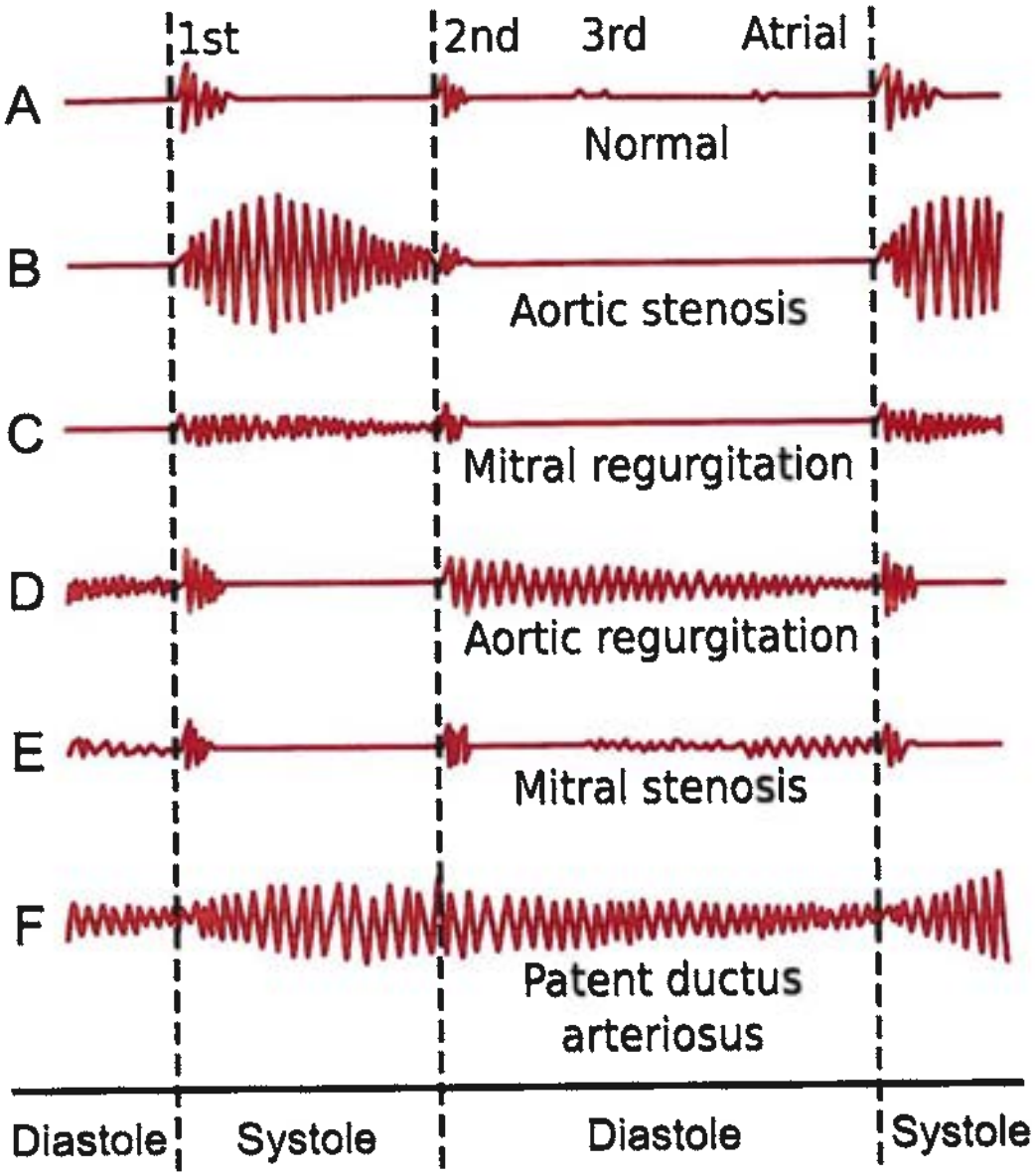
## Continuous machine-like murmur:

- PDA

**Most** murmurs of stenosis or regurgitation are **exaggerated** during **squatting** and get **softer** with the **Valsalva** manoeuvre. The exceptions are:

- **HOCM** where the **opposite** occurs and

- **Mitral valve prolapse** where the murmur **gets longer.**



# Pulses

## Pulsus paradoxus:

- **Greater than** the normal (**10 mmHg**) **fall** ↓ in systolic blood pressure during inspiration → **faint or absent pulse in inspiration**.
- Severe asthma, **cardiac tamponade**.

## Slow-rising/plateau

- **Aortic stenosis**

## Collapsing:

- **Aortic regurgitation**
- **Patent ductus arteriosus**
- Hyperkinetic (anaemia, thyrotoxic, fever, exercise/pregnancy)

## Pulsus alternans

- Regular alternation of the **force** of the arterial pulse
- **Severe LVF**

## Bisferiens pulse:

- 'Double pulse' - two systolic peaks: The first beat is the percussion wave of normal systole and the second wave is formed by recoil of the vascular bed (dicrotic wave).
- **Mixed aortic valve disease**
- **HOCM**

## 'Jerky' pulse:

- **HOCM***

*HOCM may occasionally be associated with a Bisferiens pulse

| How to read a 12-lead electrocardiogram: examination sequence | |
|---|---|
| **Rhythm strip (lead II)** | To determine heart rate and rhythm |
| **Cardiac axis** | Normal if QRS complexes +ve in leads I/II |
| **P-wave shape** | Tall P waves denote right atrial enlargement (P pulmonale) and notched P waves denote left atrial enlargement (P mitrale) |
| **PR interval** | Normal = 0.12–0.20 sec. Prolongation denotes impaired atrioventricular nodal conduction. A short PR interval occurs in Wolff–Parkinson–White syndrome |
| **QRS duration** | If > 0.12 sec, ventricular conduction is abnormal (left or right bundle branch block) |
| **QRS amplitude** | Large QRS complexes occur in slim young patients and in patients with left ventricular hypertrophy |
| **Q waves** | May signify previous myocardial infarction |
| **ST segment** | ST elevation may signify myocardial infarction, pericarditis or left ventricular aneurysm; ST depression may signify ischaemia or infarction |
| **T waves** | T-wave inversion has many causes, including myocardial ischaemia or infarction, and electrolyte disturbances |
| **QT interval** | Normal < 0.42 sec. QT prolongation may occur with congenital long QT syndrome, low K+, Mg2+ or Ca2+, and some drugs |
| **ECG conventions** | Depolarisation towards electrode: +ve deflection<br>Depolarisation away from electrode: −ve deflection<br>Sensitivity: 10 mm = 1 mV<br>Paper speed: 25 mm per sec<br>Each large (5 mm) square = 0.2 sec<br>Each small (1 mm) square = 0.04 sec<br>Heart rate = 1500/RR interval (mm) (i.e. 300 ÷ number of large squares between beats) |

# Jugular venous pulse (JVP)

As well as providing information on **right atrial pressure**, the jugular vein waveform may provide clues to underlying valvular disease.

**A non-pulsatile JVP** is seen in superior vena caval obstruction (SVCO).

**Kussmaul's sign** describes a paradoxical rise in JVP during inspiration seen in constrictive pericarditis.

## 'a' wave = atrial contraction:

- Large if atrial pressure e.g. tricuspid stenosis, pulmonary stenosis, pulmonary hypertension
- Absent if in atrial fibrillation

## Cannon 'a' waves:

- Caused by the right atrium contracting against a closed tricuspid valve.
- Whilst tricuspid stenosis may cause large 'a' waves it does not cause cannon 'a' waves.
- Are seen in complete heart block, ventricular tachycardia/ectopics, **nodal rhythm**, **single chamber ventricular pacing.**
- May be subdivided into regular or intermittent:
  - **Regular cannon waves:**
    - **VT** (with 1:1 ventricular-atrial conduction).
    - Atrio-ventricular nodal re-entry tachycardia **(AVNRT).**
  - **Irregular cannon waves:**
    - **Complete heart block.**

## 'c' wave:

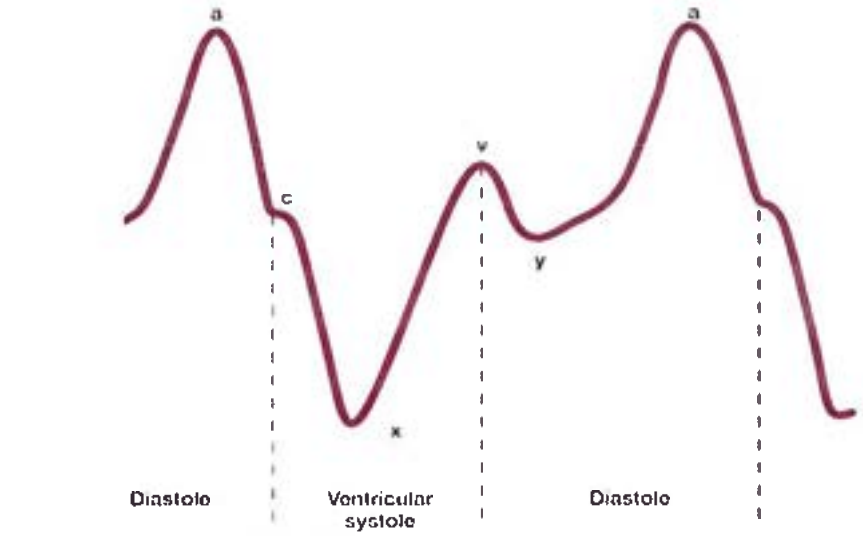
- closure of tricuspid valve
- not normally visible

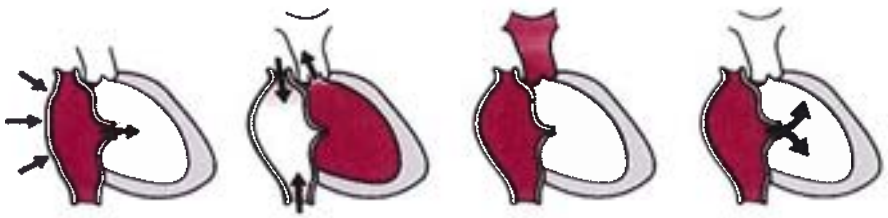
## 'v' wave:

- Due to passive filling of blood into the atrium against a closed tricuspid valve (i.e. the venous return)
- **Giant v waves** in **tricuspid regurgitation**

**'x' descent** = fall in atrial pressure during ventricular **systole**

**'y' descent** = **opening of tricuspid valve**



**a wave**
Atrium contracting tricuspid valve open

**x descent**
Atrium relaxing then filling, tricuspid closed

**v wave**
Atrium tense, full; tricuspid closed

**y descent**
Atrium emptying, tricuspid open

# ECG

## ECG: axis deviation

### Causes of right axis deviation (RAD):

- right ventricular hypertrophy
- left posterior hemiblock
- lateral myocardial infarction
- chronic lung disease → cor pulmonale
- pulmonary embolism
- ostium secundum ASD
- Wolff-Parkinson-White syndrome* - left-sided accessory pathway
- normal in infant < 1 years old
- minor RAD in tall people

### Causes of left axis deviation (LAD):

- left anterior hemiblock
- left bundle branch block
- inferior myocardial infarction
- Wolff-Parkinson-White syndrome* - right-sided accessory pathway
- hyperkalaemia
- congenital: ostium primum ASD, tricuspid atresia
- minor LAD in obese people

*in the majority of cases, or in a question without qualification, Wolff-Parkinson-White syndrome is associated with left axis deviation

## ECG: normal variants

**The following ECG changes are considered normal variants in an athlete:**

- Sinus bradycardia
- First degree heart block
- Junctional rhythm
- Wenckebach phenomenon **Hyperacute T wave** (They 'would hurt if
- you sat on them')
- **Wide QRS complex**

The most appropriate initial therapy of hyperkalaemia is **protection of the heart** by **IV calcium gluconate** which acts within **minutes** and works by **raising ↑ the depolarization threshold for myocytes**.

# ECG: coronary territories

**The table below shows the correlation between ECG changes and coronary territories:**

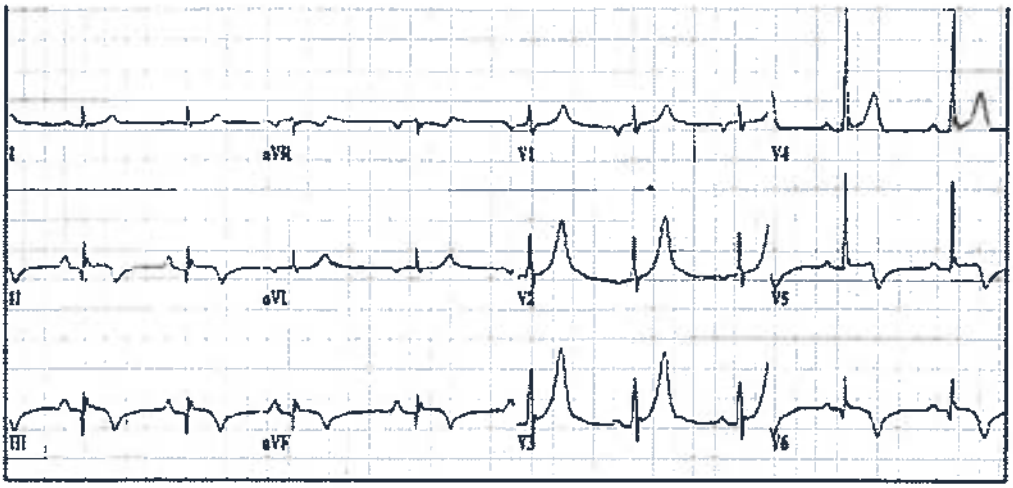
| | ECG changes | Coronary artery |
|---|---|---|
| Anterior | V1-V4 | Left anterior descending |
| Inferior | II, III, aVF | Right coronary |
| High lateral | I, aVL | First diagonal (D1) of LAD |
| Lateral | I, aVL +/- V5-6 | Left circumflex |
| Posterior | Tall R in V1-2 + ST dep. in V1-V4 | Usually left circumflex, also right coronary. |

These are classical **triple** effects findings of a **circumflex occlusion**. The table below shows how the changes correspond to the cardiac anatomy:

| ECG changes | Component of infarction |
|---|---|
| ST elevation greater in lead II than in lead III with abnormal Q waves in II, III, and aVF | **Inferior** component of infarction |
| Tall R waves in V1-2, tall and pointed T waves in V1-V3 | **Posterior** component of infarction |
| ST elevation in V5-V6 | **Lateral** component of infarction |

It should be remembered that a new left bundle branch block (LBBB) may point towards a diagnosis of acute coronary syndrome.

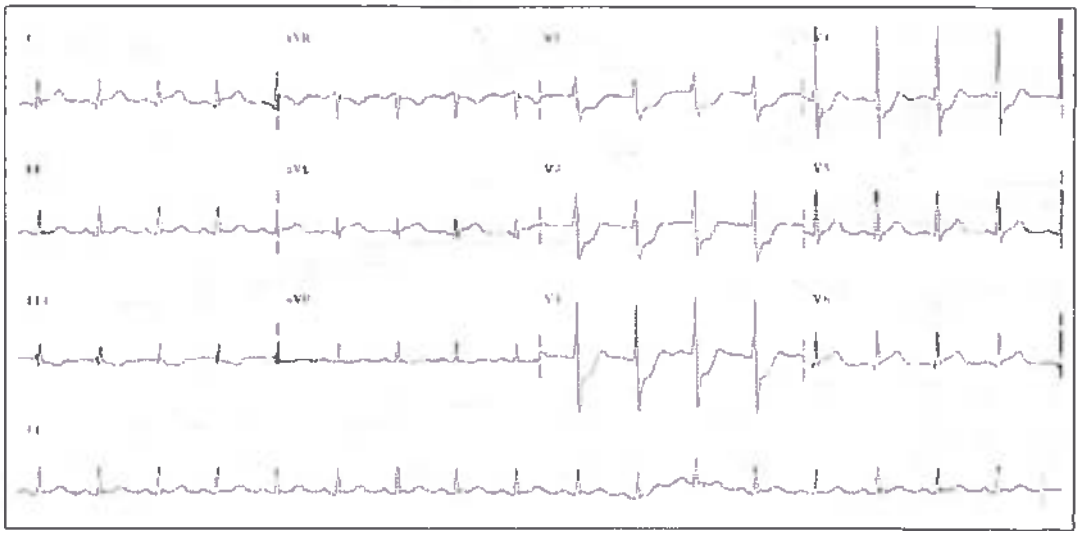
Diagram showing the correlation between ECG changes and coronary territories in acute coronary syndrome



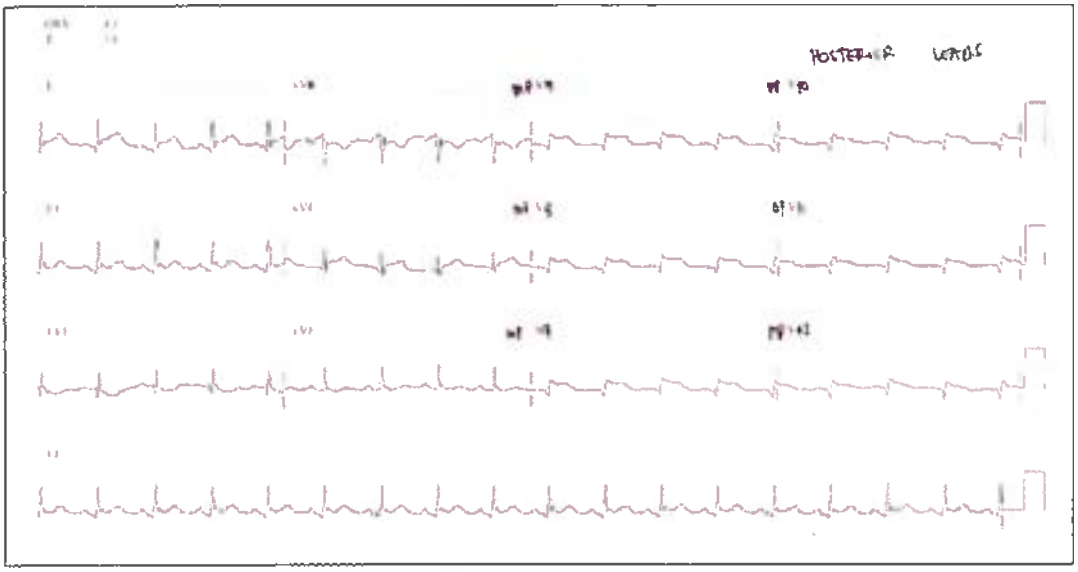

Classic ECG of Circumflex coronary artery occlusion (Inf+Post+Lat)

## Posterior MI:

ECG: ST depression in V1 to V3 with upright T waves and dominant R waves (these findings are the reverse of ECG findings of anterior MI)



The diagnosis of Posterior MI can be confirmed with **ST elevation at posterior leads V7 to V9 or V12**, as shown below:



Posterior MI is usually seen in association with **inferior** or **lateral** wall MI, but can be seen **alone in about 4% of cases**.

The majority of the posterior wall is supplied by **the left circumflex artery**, with a small portion supplied by the right coronary artery.

## Coronary circulation:

**Arterial supply of the heart:**

- Right aortic sinus → right coronary artery (RCA).
- Left aortic sinus → left coronary artery (LCA).
- **RCA → posterior descending** (in 85% it is a branch of the RCA).
- **RCA** supplies **SA node in 60%, AV node in 90%**
- LCA → LAD + circumflex
- The **left main stem** is much **shorter than 4 cm**

## Venous drainage of the heart:

- **Coronary sinus** drains into the **right atrium (RA)**

The concept of coronary dominance refers to which coronary artery supplies **the posterior descending coronary artery**.

In the case of approximately **85%** of patients this is **the right coronary artery** with about 15% of patients having a dominant left circumflex.

The **right coronary artery** supplies the **AV node**, so **bradycardia/heart block** following **inferior MI** is common and they are not considered to be of any prognostic significance.

But if **inferior** MI with **bradycardia** + **junctional rhythm** with **wide QRS** (duration 160 ms) >>> indicates a more **extensive** ischaemic territory affecting the conducting bundle >>> **Temporal pacing** can be used as a holding measure to allow the myocardium time to recover.

However, **heart block** following **anterior** MI is a grave prognostic marker as this indicates a **large anterior** wall **extensive** infarction.

The **right coronary** system also supplies the **right ventricle**, hence problems relating to a **RV infarct** are commonly associated with an **inferior MI**.

**NB**: Pt. with MI + complete heart block >>> so, the right coronary artery is affected as it supplies the atrioventricular node (**AVN**) in **90%** of patients.

**NB: RCA** lesion >>> think of **4** >>> **Inferior** MI ± **Posterior** MI ± **RV** infarction ± **Heart block.**

**NB**: **Inferior MI** + **Complete heart block** (HR 40/min) + **Low BP** (80/50 mmHg) + ↑ **JVP** >>> so **RV infarction** >>> **Treatment**: **IV fluids** to optimize RV filling pressure, if persistent hypotension give **inotropes**.

# ECG: PR interval

## Causes of a prolonged PR interval

- idiopathic
- **ischaemic heart disease**
- **digoxin toxicity**
- **hypokalaemia***
- **rheumatic fever**
- **aortic root pathology** e.g. abscess secondary to endocarditis
- **Lyme disease**
- **sarcoidosis**
- **myotonic dystrophy**

A prolonged PR interval may also be seen in athletes

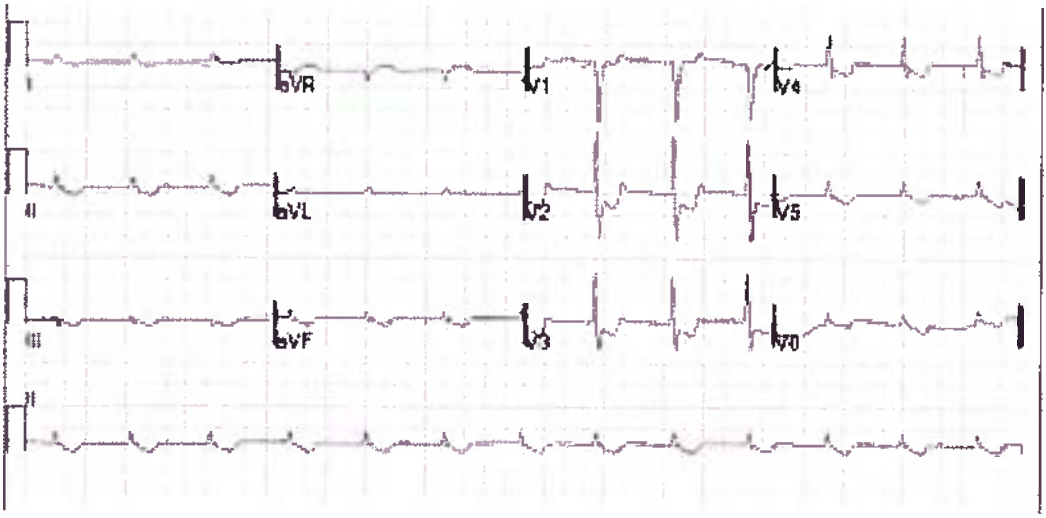
**A short PR interval is seen in Wolff-Parkinson-White syndrome**

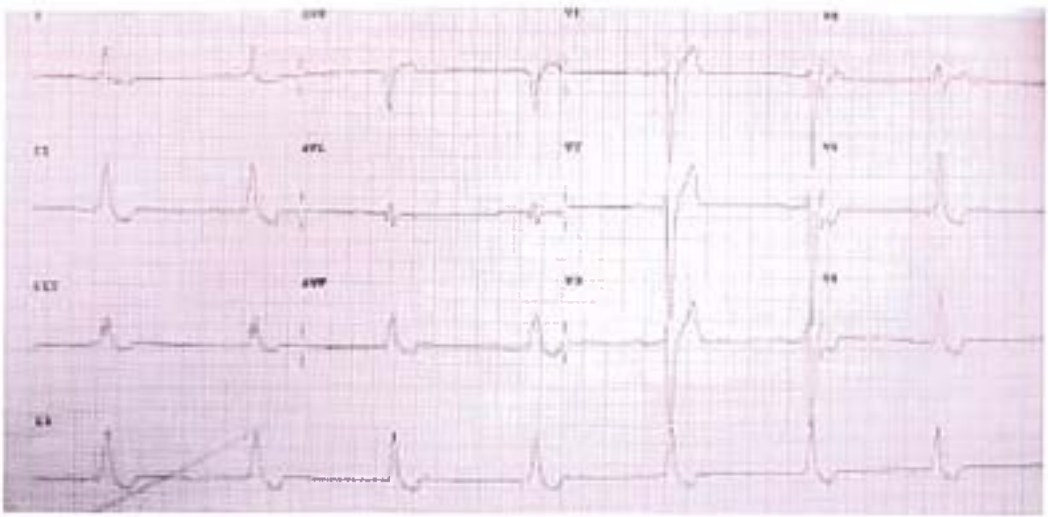
*hyperkalaemia can rarely cause a prolonged PR interval, but this is a much less common association than hypokalaemia

# ECG: digoxin

## ECG features

- down-sloping ST depression ('reverse tick', 'scooped out')
- flattened/inverted T waves
- short QT interval
- arrhythmias e.g. AV block, bradycardia

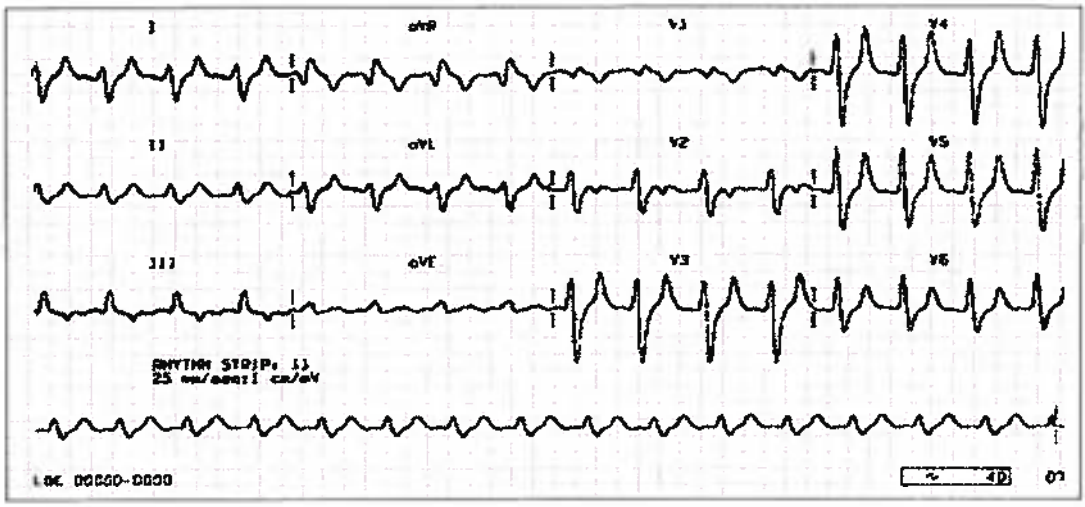


The ECG below shows typical U waves. Note also the borderline PR interval.

# ECG: hyperkalaemia

## ECG of Hyperkalaemia:

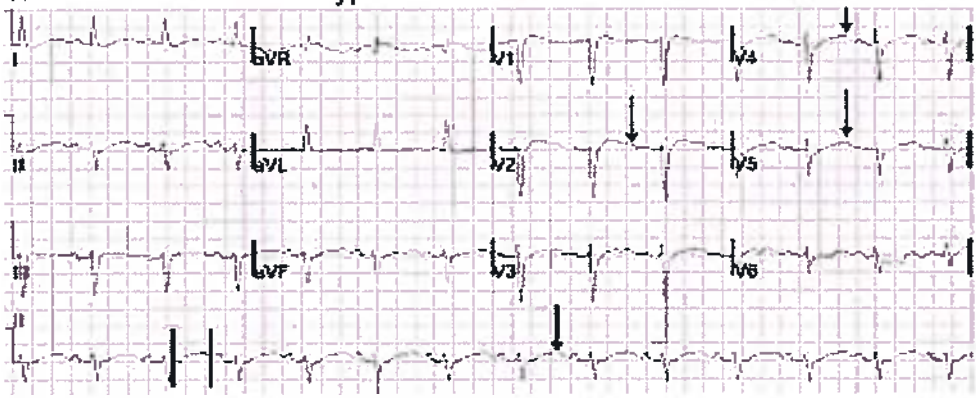


# ECG: hypokalaemia

## ECG features of hypokalaemia (serum K < 3 mmol/l):

- **Prolong PR interval**
- **ST depression**
- Small or absent/**flat T waves** (occasionally **inversion**)
- **U waves**
- **Long QT**

The ECG below shows typical U waves. Note also the borderline PR interval.



**One registered user suggests the following rhyme**

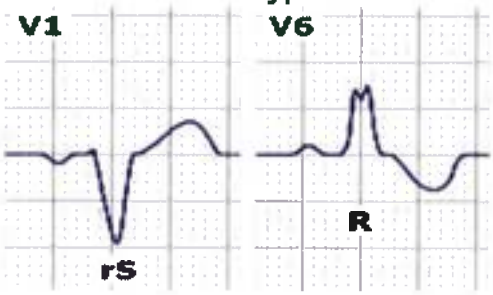
In Hypokalaemia, **U have no Pot and no T, but a long PR and a long QT**

Remember: **J** waves are seen in **hypothermia**, whilst **delta** waves are associated with **Wolff Parkinson White syndrome**.

The **causes of prominent U wave (late repolarization):** **Hypokalaemia, Cardiovascular drugs** like e.g. digitalis, amiodarone, quinidine, and **psychotropic drugs** like e.g. phenothiazines, TCA.

## ECG: left bundle branch block (LBBB)

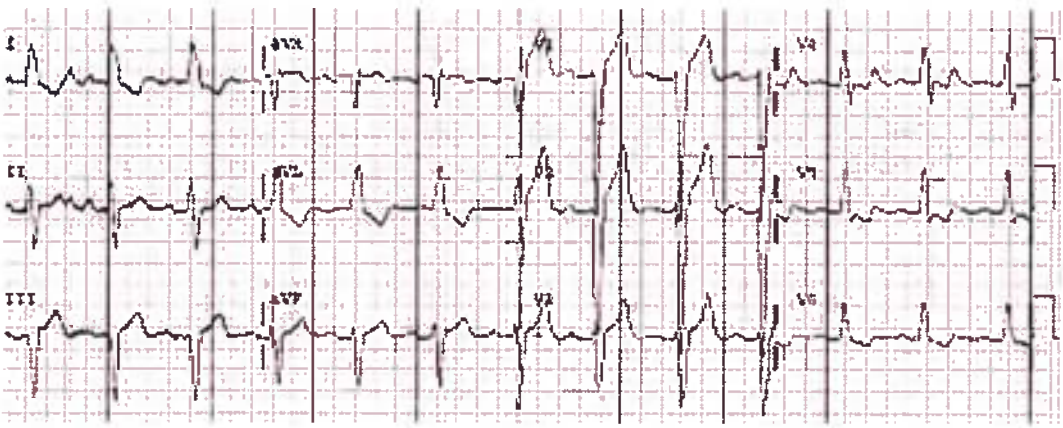
**The diagram below shows the typical features of (LBBB):**




- In LBBB there is a **'W'** in V1 and a **'M'** in V6.
- In RBBB there is a **'M'** in V1 and a **'W'** in V6.

One of the most common ways to remember the difference between LBBB and RBBB is **WiLLiaM MaRRoW**

ECG showing typical features of LBBB



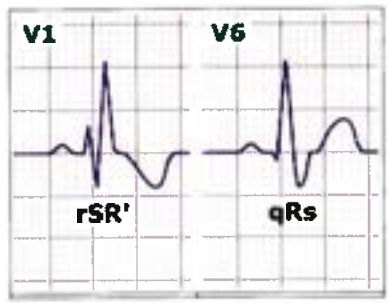
**New LBBB is always pathological**. Causes of LBBB include:

- myocardial infarction
  - diagnosing a myocardial infarction for patients with existing LBBB is difficult
  - rhe Sgarbossa criteria can help with this - please see the link for more details
- **Ischaemic heart disease**
- **Cardiomyopathy**
- **Hypertension**
- **Aortic stenosis**
- **Idiopathic fibrosis**

**NB**: **Atrial septal defects**, both primum and secundum, are associated with **RBBB** rather than LBBB.

## ECG: right bundle branch block

Right bundle branch block is a common feature seen on ECGs.




One of the most common ways to remember the difference between LBBB and RBBB is WiLLiaM MaRRoW

- in LBBB there is a 'W' in V1 and a 'M' in V6
- in RBBB there is a 'M' in V1 and a 'W' in V6

### Causes of RBBB

- normal variant - more common with increasing age
- right ventricular hypertrophy
- chronically increased right ventricular pressure - e.g. cor pulmonale
- pulmonary embolism
- myocardial infarction
- atrial septal defect (ostium secundum)
- cardiomyopathy or myocarditis

## ECG: P wave changes

**Increased P wave amplitude**

- cor pulmonale

**Broad, notched (bifid) P waves**

- often most pronounced in lead II
- a sign of left atrial enlargement, classically due to mitral stenosis

In atrial fibrillation, there is an absence of P waves.

## ECG: T wave changes

### Peaked T waves

- hyperkalaemia
- **myocardial ischaemia**

### Inverted T waves

- **myocardial ischaemia**
- **digoxin toxicity**
- **subarachnoid haemorrhage**
- **arrhythmogenic right ventricular cardiomyopathy**
- **pulmonary embolism** ('S1Q3**T3**')
- Brugada syndrome

## Peri-arrest rhythms: tachycardia

### Tachycardia:

The 2015 Resuscitation Council (UK) guidelines have simplified the advice given for the management of peri-arrest tachycardias.

Separate algorithms for the management of broad-complex tachycardia, narrow complex tachycardia and atrial fibrillation have been replaced by one unified treatment algorithm.

Following basic ABC assessment, patients are classified **as being stable or unstable** according to the presence of **any adverse signs**:

- **Shock**: hypotension (SBP < 90 mmHg), pallor, sweating, cold, clammy extremities, confusion or impaired consciousness.

- **Syncope**
- **Myocardial ischaemia**
- **Heart failure**

If any of the above adverse signs are present then **synchronised DC shocks** should be given.

Treatment following this is given according to whether the QRS complex is narrow or broad and whether the rhythm is regular or irregular.

The full treatment algorithm can be found at the Resuscitation Council website, below is a very limited summary:

## Broad-complex tachycardia:

### Regular:

- Assume **ventricular tachycardia** (unless previously confirmed SVT with bundle branch block)
- loading dose of amiodarone followed by 24 hour infusion.

### Irregular:

- seek expert help. Possibilities include:
  - atrial fibrillation with bundle branch block - the most likely cause in a stable patient
  - atrial fibrillation with ventricular pre-excitation
  - torsade de pointes

## Narrow-complex tachycardia:

### Regular:

- Vagal manoeuvres followed by IV adenosine
- If above unsuccessful consider diagnosis of atrial flutter and control rate (e.g. Beta-blockers)

### Irregular:

- Probable atrial fibrillation
- If onset < 48 hr. consider electrical or chemical cardioversion
- Rate control (e.g. Beta-blocker or digoxin) and
- Anticoagulation

# Peri-arrest rhythms: bradycardia

The 2015 Resuscitation Council (UK) guidelines emphasise that the management of bradycardia depends on:

- Identifying the presence of signs indicating haemodynamic compromise - **'adverse signs': see before.**
- Identifying **the potential risk of asystole**

## Adverse signs

The following factors indicate haemodynamic compromise and hence the need for treatment:

- shock: hypotension (systolic blood pressure < 90 mmHg), pallor, sweating, cold, clammy extremities, confusion or impaired consciousness
- syncope
- myocardial ischaemia
- heart failure

**Atropine (500mcg IV)** is the first line treatment in this situation.

If there is an unsatisfactory response the following interventions may be used:

- atropine, up to maximum of 3mg
- transcutaneous pacing
- isoprenaline/adrenaline infusion titrated to response

Specialist help should be sought for consideration of transvenous pacing if there is no response to the above measures.

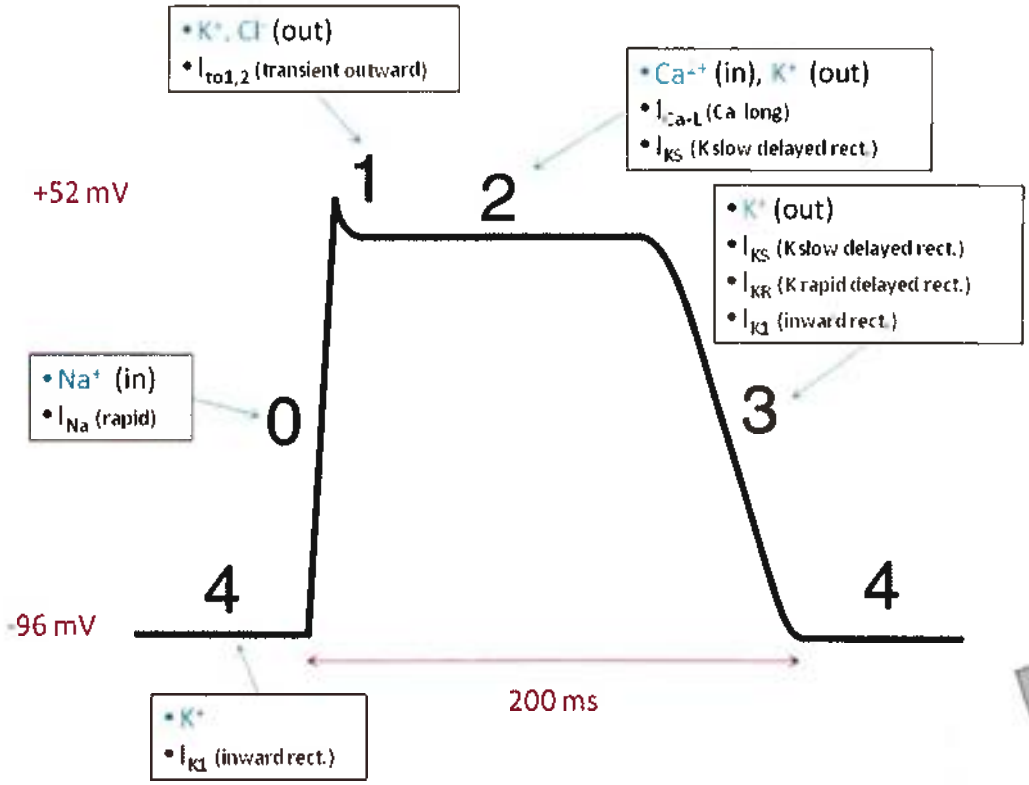
## Potential risk of asystole:

**The following indicate a potential risk of asystole and hence the need for treatment with transvenous pacing:**

- **Complete heart block with *broad* complex QRS**
- **Mobitz type II AV block**
- **Recent asystole**
- **Ventricular pause > 3 seconds**

If there is a delay in the provision of transvenous pacing the following interventions may be used:

**NB**: Complete heart block with a narrow complex QRS complex carries the least risk of asystole as the atrioventricular junctional pacemaker may provide a haemodynamically acceptable and stable heart rate.




| Phase | Description | Mechanism |
|---|---|---|
| 0 | Rapid depolarisation | Rapid sodium influx<br>These channels automatically deactivate after a few ms |
| 1 | Early repolarisation | Efflux of potassium |
| 2 | **Plateau** | **Slow influx of calcium** + Efflux of potassium |
| 3 | Final repolarisation | Efflux of potassium |
| 4 | Restoration of ionic concentrations | Resting potential is restored by $Na^+/K^+$ ATPase<br>There is slow entry of $Na^+$ into the cell decreasing the potential difference until the threshold potential is reached, triggering a new action potential |

**NB**: cardiac muscle remains contracted 10-15 times longer than skeletal muscle.

**Conduction velocity:**

| Site | Speed |
|---|---|
| Atrial conduction | Spreads along ordinary atrial myocardial fibres at 1 m/sec |
| AV node conduction | **0.05** m/sec |
| Ventricular conduction | Purkinje fibres are of large diameter and achieve velocities of **2-4 m/sec**. **Purkinje fibres have the highest conduction velocity of all cardiac tissue types** (this allows a rapid and coordinated contraction of the ventricles). |

## ECG: hypothermia

- Bradycardia
- First degree heart block
- **'J' wave** - small positive deflection hump at the end of the QRS complex, it is highly **sensitive** and **specific** for hypothermia.
- **Long QT interval**
- Atrial and ventricular arrhythmias

## ECG: ST elevation

### Causes of ST elevation:

- Myocardial infarction
- Pericarditis
- Left ventricular aneurysm post MI
- Prinzmetal's angina (coronary artery spasm)
- **Normal variant - 'high take-off' " early repolarization"**
- Rare: subarachnoid haemorrhage, part of spectrum of changes in hyperkalaemia

## ECG: ST depression

### Causes of ST depression:

- **Secondary to** abnormal QRS (LVH, LBBB, RBBB)
- **Ischaemia**
- **Syndrome X**
- **Digoxin**
- **Hypokalaemia**

## SSS (Sick Sinus Syndrome) = Sinus Node Disease (SND) = (tachy-brady syndrome)

**Usually occurs** in **old patients** with attacks of symptomatic bradycardia with dizziness, syncope and headedness.

**Also, this sinus bradycardia** may be associated with **episodes of AF.**
Also, may be associated with **sinus pause (sinus arrest), up to 2 seconds may be accepted.**

**Treatment:** Dual chamber pacemaker.
If patient only has a VVI pacemaker in situ, it will prevent bradycardia-induced syncope but may be presented with symptomatic fast AF.

**If patient develops rapid AF** >>> treatment is initially to **cardiovert** this patient then the **pacemaker function and settings should be rechecked** after cardioversion, subsequently the patient should be treated with **antiarrhythmic** medication to prevent recurrences of fast AF.

**DC cardioversion** is not contraindicated in patients with pacemakers.
**If patient is on long** time high dose of beta blocker, so gradual withdrawal of βB to avoid rebound tachycardia.

# Arrhythmias

## Investigating palpitations

Palpitations are a common presenting symptom.

### Possible causes include

- arrhythmias
- stress
- increased awareness of normal heart beat / extrasystoles

### First-line investigations include:

- 12-lead ECG: this will only capture the heart rhythm for a few seconds and hence is likely to miss episodic arrhythmias. However, other abnormalities linked to the underlying arrhythmia (for example a prolonged QT interval or PR interval, or changes suggesting recent myocardial ischaemia) may be seen.
- thyroid function tests: thyrotoxicosis may precipitate atrial fibrillation and other arrhythmias
- urea and electrolytes: looking for disturbances such as a low potassium
- full blood count

### Capturing episodic arrhythmias

First-line investigations are often normal in patients complaining of palpitations. The next step is to exclude an episode arrhythmia.

#### The most common investigation is Holter monitoring

- portable battery operated device
- continuously records ECG from 2-3 leads
- usually done for 24 hours but may be used for longer if symptoms are less than daily
- patients are asked to keep a diary to record any symptomatic palpitations. This can later be compared to the rhythm strip at the time of the symptoms
- at the end of the monitoring a report is generated summarising a number of parameters including heart rate, arrhythmias and changes in ECG waveform

#### If no abnormality is found on the Holter monitor, and symptoms continue, other options include:

- external loop recorder
- implantable loop recorder

# Arrythmias and Related Disorders

## Long QT syndrome (LQTS)

LQTS is an inherited condition associated with **delayed repolarization of the ventricles**.
It is important to recognise as it may lead to **ventricular tachycardia (VT)** and can therefore cause collapse/sudden death.
The most common variants of LQTS (LQT1 & LQT2) are caused by defects in the alpha subunit of the slow delayed rectifier **potassium channel**.
A normal corrected QT interval is less than **430 ms (0.43 Sec.) in males** and **450 ms (0.45 Sec.) in females**.

Normal range for duration of the **corrected QT interval (QTc)** is **350 -430 ms**

### Causes of a prolonged QT interval:

**Causes of Prolonged QT Interval**

Antiarrhythmic drugs (e.g., amiodarone, sotalol, quinidine, procainamide, ibutilide, dofetilide, flecainide)
Psychiatric medications, particularly overdoses (tricyclic antidepressants, antipsychotic agents)
Certain antibiotics (e.g., macrolides, fluoroquinolones, antifungals, antimalarials)
Certain antihistamines (e.g., diphenhydramine, astemizole, loratadine, terfenadine)
Electrolyte abnormalities (e.g., hypocalcemia, hypokalemia, hypomagnesemia)
Raised intracranial pressure ("cerebral t waves")
Hypothermia
Hypothyroidism

**Congenital long-QT syndrome**

- Jervell-Lange-Nielsen (JLN) syndrome: (includes **deafness** and is due to an abnormal potassium channel)
- Romano-Ward syndrome: (no deafness)

**Jervell - Lange-Nielsen (JLN) syndrome** is caused by **mutations** in the **KCNE1** and **KCNQ1** genes.
The KCNE1 and KCNQ1 genes provide instructions for making proteins that work together to form a channel across cell membranes. These channels transport positively charged **potassium** atoms (ions) out of cells. The movement of potassium ions through these channels is critical for maintaining the normal functions of **inner ear structures** and **cardiac muscle**.

## Features:

- **May be** picked up on routine ECG or following family screening.
- **Long QT1** - usually associated with exertional syncope, often **swimming.**
- **Long QT2** - often associated with syncope occurring following **emotional** stress, exercise or auditory stimuli e.g. doorbell or telephone ring.
- **Long QT3** - events often occur at **night** or at **rest.**
- **Sudden** cardiac death.
- **Diagnosis** is based upon the **QTc (corrected QT interval)**, although this may be within the normal range at rest; hence **Holter ECG monitoring** is recommended.
- **Identification of an LQTS genetic mutation** confirms the diagnosis. However, a negative result on genetic testing is of limited diagnostic value because **only** approximately **50%** of patients with LQTS have known mutations. The remaining half of patients with LQTS may have mutations of yet **unknown** gene.

**Therefore, genetic testing of LQTS has high specificity but a low sensitivity.**

The ECG shows a long QT and ventricular premature beats. The loss of consciousness may have been due to ventricular arrhythmia, in particular, torsade de pointes VT.

## Management (by order)

- **Avoid drugs** which prolong the QT interval and other **precipitants** if appropriate (e.g. Strenuous exercise).
- **Beta-blockers** (e.g. Propranolol, Metoprolol & Atenolol, **NOT Sotalol**).
- **ICD** (Implantable cardioverter defibrillators) in **high risk cases (i.e. It is only required in high risk cases, for example if the patient has a QTc > 500ms or previous episodes of cardiac arrest.**
- **Left stellate cardiac ganglionectomy.**

**Long QT syndrome. >> usually due to loss-of-function/blockage of K+ channels.**

**NB: Beta blockers** are the **mainstay** of therapy for **asymptomatic** as well as **symptomatic** patients with idiopathic LQTS.
Beta blockers decrease sympathetic activation from the left stellate ganglion, also decrease the maximal heart rate achieved during exertion and thereby prevent exercise-related arrhythmic events that occur in LQTS.

Patients who experience ventricular arrhythmias or aborted SCD despite beta blocker therapy >>> should have an **ICD** in addition to **βB**.

**Left stellate cardiac ganglionectomy** is an invasive procedure and results in Horner's syndrome. It is performed in patients who have symptoms despite βB and have frequent shocks with ICD.

**NB**: Non-sedating antihistaminics are classic cause of prolonged QT in a patient, especially if also taking P450 enzyme inhibitor, e.g. Patient with a cold takes terfenadine and erythromycin at the same time.

**NB**: **Sotalol** may **exacerbate long QT syndrome** (due to blockage of K channel) it leads to a risk of ventricular arrhythmias. This can be a particular risk in individuals with **hypokalaemia**. So **Sotalol is better to be avoided in patients with thiazide diuretics.**

**EX**: A 75-year-old man with a history of anterior MI is taking amiodarone 400 mg/day for history of VT. He has a prolonged QTc interval on his ECG of 550 ms. The most appropriate management >>> **Stop amiodarone immediately and can replace with atenolol 50 mg a day.**

## Management of drug-induced LQTS is:

- **Stop** precipitating drugs.
- Correction of any **electrolyte** disturbance like hypo K or Mg.
- **Treatment** of associated ventricular arrhythmia: first line for drug-induced LQTS is **IV MgSO4** 2 gm as bolus over 1-2 minutes, followed by another bolus in 15 minutes if required, or continuous infusion at a rate of 5-20 mg/min.

**QT shortening**: caused by: >>> **Hypercalcaemia**, **Hypermagnesemia**, **Digoxin**, or **Thyrotoxicosis**

## Torsade's de pointes

Torsade's de pointes ('twisting of the points') is a rare arrhythmia associated with a long QT interval.

It may deteriorate into ventricular fibrillation and hence lead to sudden death.

### Causes of long QT interval:

- congenital
  - Jervell-Lange-Nielsen syndrome
  - Romano-Ward syndrome
- antiarrhythmics: amiodarone, sotalol, class 1a antiarrhythmic drugs
- tricyclic antidepressants
- antipsychotics
- chloroquine
- terfenadine
- erythromycin
- electrolyte: hypocalcaemia, hypokalaemia, hypomagnesaemia
- myocarditis
- hypothermia
- subarachnoid haemorrhage

**Risk factors:** **female sex**, **prolonged QT interval**,CHF, digitalis toxicity, recent conversion from AF.

**Management:** **IV MgSo4** (Magnesium Sulphate)
MgSo4 >>> **it decreases Ca influx,** reducing the amplitude of the VT and helping terminate runs of torsades. It is effective **even when serum magnesium level is normal.**

ECG showing torsades de pointes

# Arrhythmogenic right ventricular cardiomyopathy

Arrhythmogenic right ventricular cardiomyopathy (ARVC, also known as arrhythmogenic right ventricular dysplasia or ARVD) is a form of inherited cardiovascular disease which may present with syncope or sudden cardiac death.
It is generally regarded as the **second most common cause of sudden cardiac death** in the young after hypertrophic cardiomyopathy.
Although ARVC was initially described in the right ventricle, most patients have biventricular involvement.

## Pathophysiology

- inherited in an autosomal dominant pattern with variable expression
- the **right ventricular myocardium is replaced by fatty and fibrofatty tissue**
- around 50% of patients have a mutation of one of the several genes which encode components of desmosome

## Presentation

- palpitations
- syncope
- sudden cardiac death

## Investigation

- **ECG abnormalities in V1-3, typically T wave inversion.** An epsilon wave is found in about 50% of those with ARV - this is best described as a terminal notch in the QRS complex
- echo changes are often subtle in the early stages but may show an enlarged, hypokinetic right ventricle with a thin free wall
- magnetic resonance imaging is useful to show fibrofatty tissue

## Management

- drugs: sotalol is the most widely used antiarrhythmic
- catheter ablation to prevent ventricular tachycardia
- implantable cardioverter-defibrillator

## Naxos disease

- an autosomal recessive variant of ARVC
- a triad of ARVC, palmoplantar keratosis, and woolly hair

# Ventricular tachycardia (VT)

Whilst a broad complex tachycardia may result from a supraventricular rhythm with aberrant conduction, the European Resuscitation Council advise that in a peri-arrest situation it is assumed to be ventricular in origin.

VT is broad-complex tachycardia originating from a ventricular ectopic focus.

It has the potential to precipitate ventricular fibrillation and hence requires urgent treatment.

## There are two main types of VT:

- **Monomorphic VT:** most commonly caused by myocardial infarction.
- **Polymorphic VT:** A subtype of polymorphic VT is **torsade's de pointes** which is **precipitated by prolongation of the QT interval.**

## Causes of a prolonged QT interval

| Congenital | Drugs | Other |
|---|---|---|
| • Jervell-Lange-Nielsen syndrome (includes deafness and is due to an abnormal potassium channel)<br>• Romano-Ward syndrome (no deafness) | • amiodarone, sotalol, class 1a antiarrhythmic drugs<br>• tricyclic antidepressants, fluoxetine<br>• chloroquine<br>• terfenadine<br>• erythromycin | • electrolyte: hypocalcaemia, hypokalaemia, hypomagnesaemia<br>• acute myocardial infarction<br>• myocarditis<br>• hypothermia<br>• subarachnoid haemorrhage |

## Management:

If the patient has adverse signs (systolic BP < 90 mmHg, chest pain, heart failure or rate > 150 beats/min) then **immediate cardioversion is** indicated.

In the absence of such signs **antiarrhythmics** may be used. If these fail, then electrical cardioversion may be needed with **synchronised DC shocks.**

VT with pulse (not respond to medical ttt) >>> cardioversion (**synchronized**)
Pulseless VT or VF >>> DC (**asynchronized**)

**Drug therapy:**

- **Amiodarone**: ideally administered through a central line (300 mg over the first hour then 900 over the next 23 hours).
- **Lidocaine**: use with caution in severe left ventricular impairment as it is negative inotropic drug.
- **Procainamide**.

**NB**: Verapamil should NOT be used in VT.

**If drug therapy fails:**

- Electrophysiological study **(EPS)**.
- Implantable cardioverter-defibrillator **(ICD)** - this is particularly indicated in patients with significantly impaired LV function.

**NB**: **Hypokalaemia** is the most important cause of ventricular tachycardia (VT) clinically, followed by **hypomagnesaemia**.

**Severe hyperkalaemia** may cause VT in certain circumstances, for example in patients with structural heart disease

**NB**: Pulseless VT with **severe hypothermia** ⊗ >>> DC shock or medication will be ineffective, so better **to start with prolonged CPR firstly** till temperature can reach > 30°.

Hypothermic patients do not respond well to shocks or drugs and if there is no response to the first three shocks the patient **should be rewarmed** to at least 32°C **before** any drugs or shocks are administered.

**NB**: **PVC** to be significant, they have to meet the following criteria:

- Frequency **≥ 6 bpm**.
- PVC in **bigeminal** or **trigeminal** rhythm.
- PVC in **short runs of VT**
- PVC exhibiting **R on T phenomenon**.
- PVC associated with serious **organic** heart disease and **LV decompensation**.

# Heart block (HB)

## Features:

- **Syncope**
- **Regular bradycardia (30-50 bpm)**
- Heart failure
- Wide pulse pressure
- JVP: **cannon waves** in neck
- **Variable intensity of S1**

## Types of heart block:

### First degree heart block:

- PR interval > 0.2 seconds.
- asymptomatic first-degree heart block is relatively common and does not need treatment

### Second degree heart block:

- **Type 1** (Mobitz I, Wenckebach): progressive prolongation of the PR interval until a dropped beat occurs.
- **Type 2** (Mobitz II): PR interval is constant but the P wave is often not followed by a QRS complex.

### Third degree (complete) heart block:

- There is no association between the P waves and QRS complexes.

**Mobitz type II** or **complete heart block** does **not** respond to atropine >>> the optimal **Treatment** is **Trans-venous permanent pacing.**

Atropine may be useful for sinus or junctional bradycardia.

Complete heart block following a MI >>> so, **right** coronary artery lesion.
**CHB**: There are P waves which show no relation to the QRS complexes. The QRS complexes are wide, regular and represent a ventricular escape rhythm.

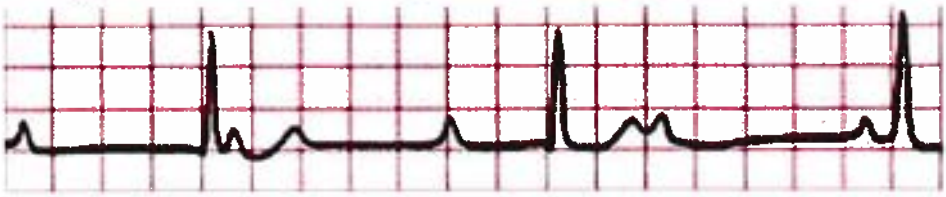
**First degree AV block**

**Second degree AV block (Mobitz I or Wenckebach)**

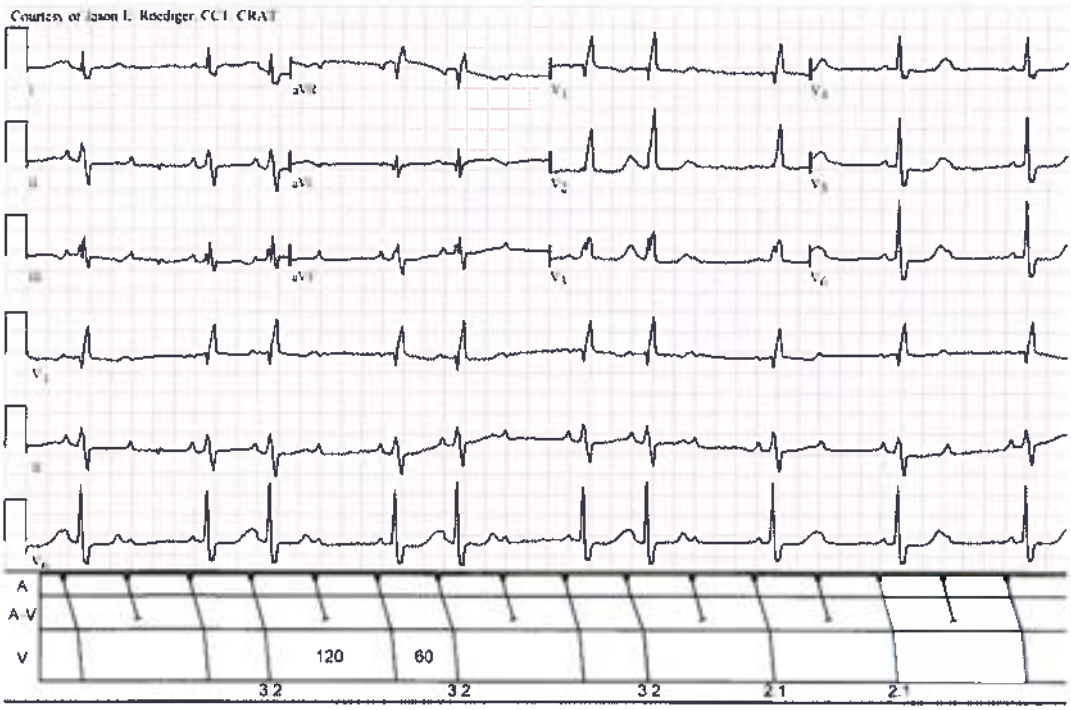
**Second degree AV block (Mobitz II)**

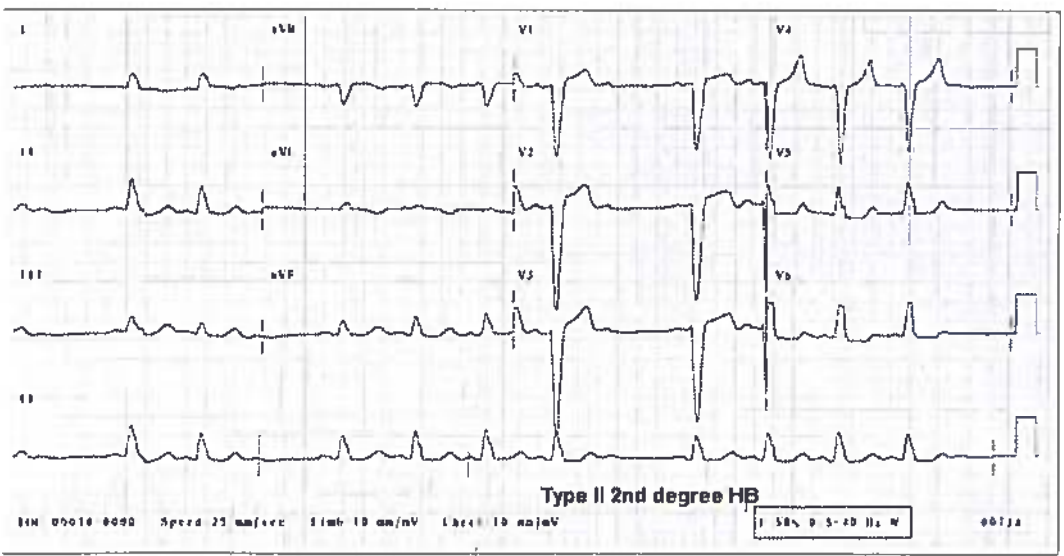
**Second degree AV block (2:1 block)**

**Third degree AV block with junctional escape**

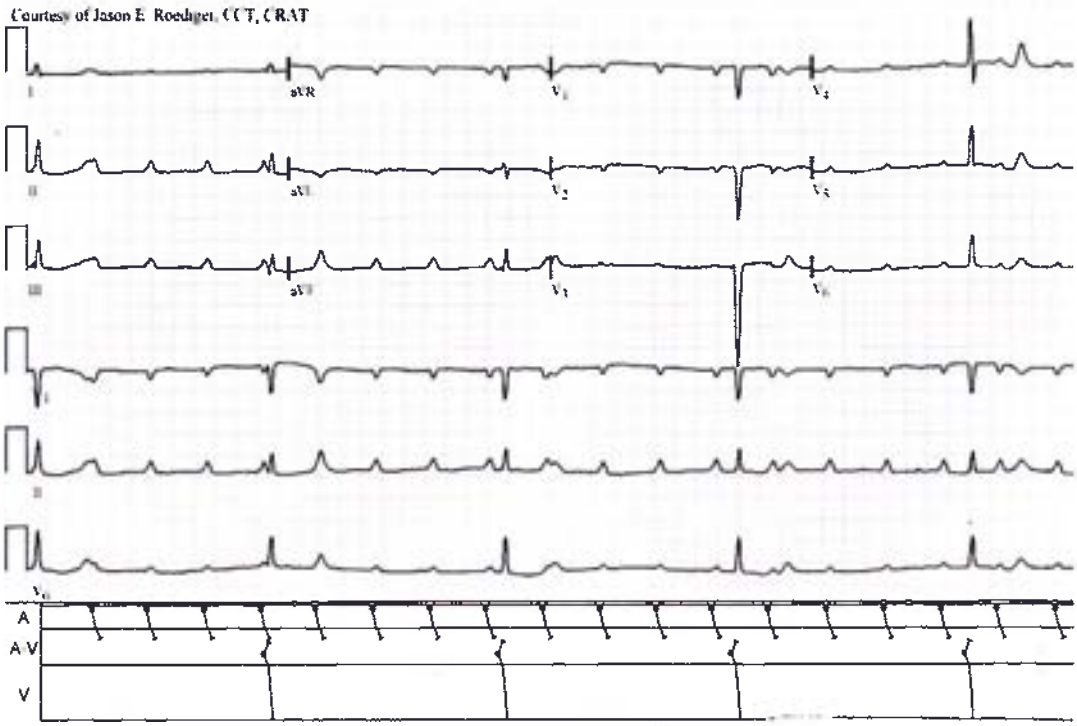


ECG showing types of heart block




**Type 1**




Sinus tachycardia with complete AV block and resulting junctional escape

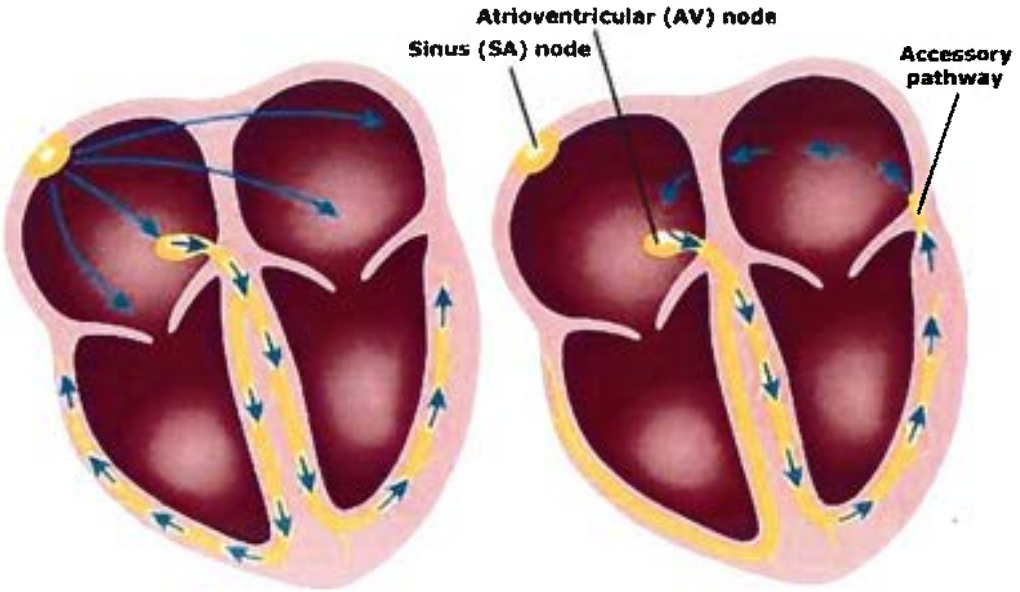
**NB: The atrioventricular node (AVN)** is supplied by the **posterior interventricular** artery, which in the **majority** of patients is a branch of the **right** coronary artery. In the remainder of patients the posterior interventricular artery is supplied by the **left circumflex artery.**

**NB:** Second degree (Type 2) and third degree HB >>> **Permanent pacing.**

## Wolf-Parkinson White Syndrome

It is caused by a **congenital accessory** conducting pathway between the atria and ventricles leading to an atrioventricular re-entry tachycardia **(AVRT).**

As the accessory pathway does not slow conduction AF can degenerate rapidly to VF.

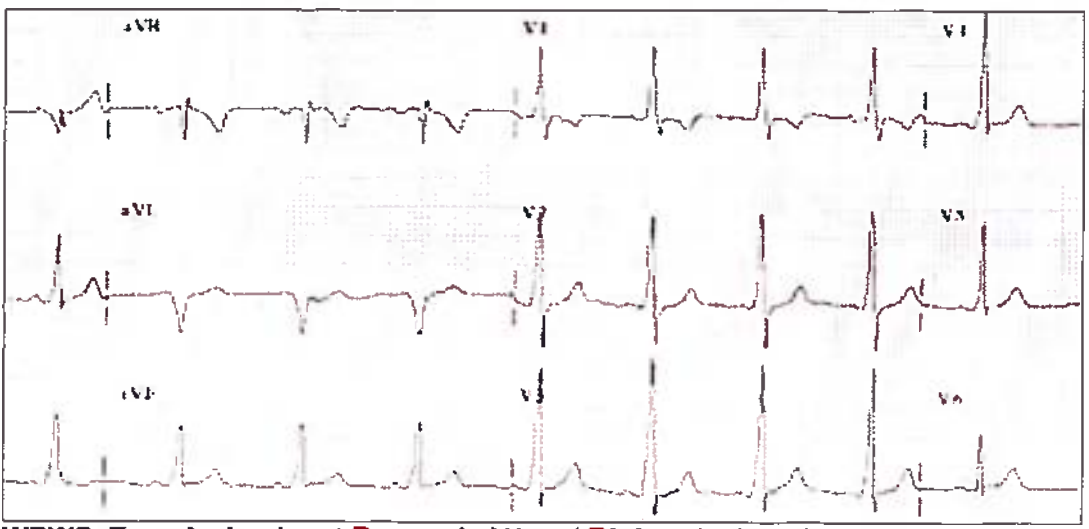



**Normal electrical pathways**

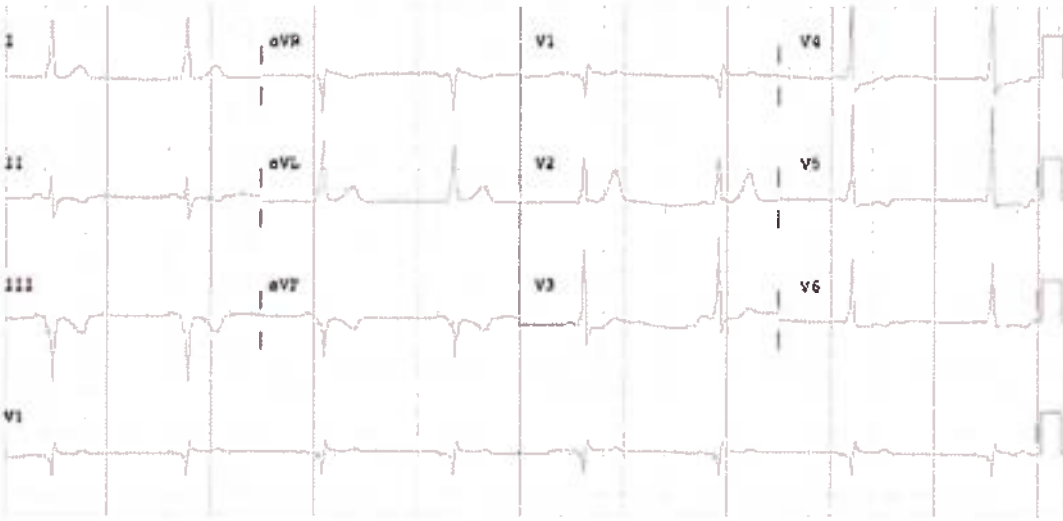
**Abnormal electrical pathway in Wolff-Parkinson-White syndrome**

## Possible ECG features include:

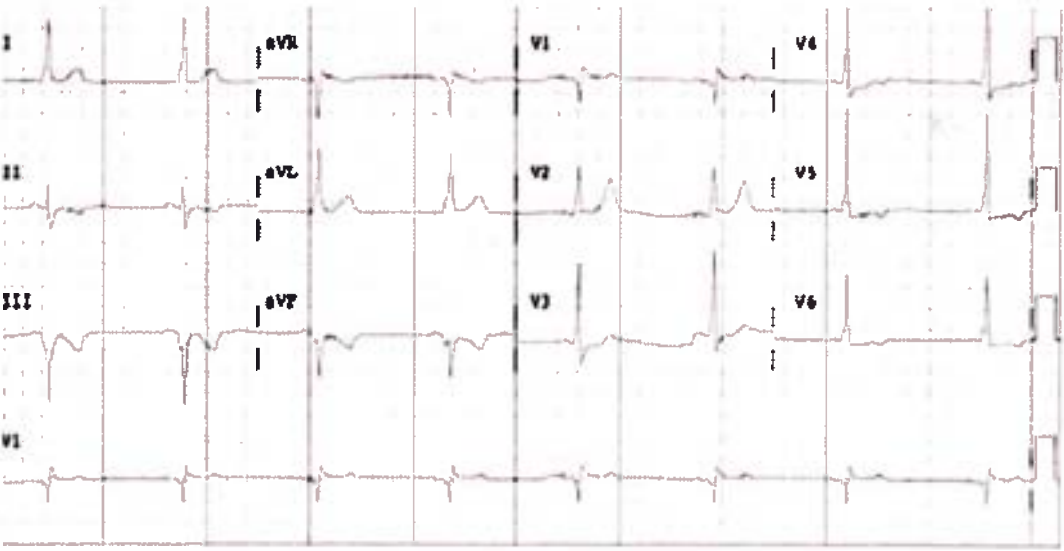
- **Short PR interval**
- **Wide QRS complexes** with **a slurred upstroke - 'delta wave'**
- Right axis deviation if left-sided accessory pathway*
- Left axis deviation if right-sided accessory pathway*



**WPWS**: Type **A**: **dominant R wave in V1** and **Right** axis deviation:




ECG showing short PR interval associated with a slurred upstroke (delta wave). Note the non-specific ST-T changes which are common in WPW and may be mistaken for ischemia. The left axis deviation means that this is type B WPW, implying a right-sided pathway




**WPWS:** Type **B**: no dominant R wave in V1, right-sided pathway, left axis deviation.

**Note the non-specific ST-T changes which are common in WPW and may be mistaken for ischaemia.**

## Differentiating between type A and type B

- Type **A** (left-sided pathway): **dominant R wave in V1**
- Type B (right-sided pathway): no dominant R wave in V1

## Associations of WPW: (5):

1) **HOCM.**
2) Mitral valve prolapse **(MVP).**
3) **Ebstein's** anomaly.
4) **Thyrotoxicosis**
5) **Secundum ASD**

## Management:

- **Definitive** treatment >>> **EPS** with **radiofrequency ablation (RFA)** of the **accessory** pathway.
- **Medical** therapy: **Flecainide**, Amiodarone, Atenolol, Sotalol.

If **not symptomatic** (no palpitations or headedness) >>> so **reassurance**.

Anticoagulation is not indicated.

Risk of arrhythmia after ablation is of the order of 7% over 5 years.

In the majority of cases, or in a question without qualification, Wolff-Parkinson-White syndrome is associated with left axis deviation.

**NB: Sotalol** should be avoided if there is **coexistent atrial fibrillation** as prolonging the refractory period at the AV node may increase the rate of transmission through the accessory pathway, increasing the ventricular rate and potentially deteriorating into ventricular fibrillation.

**NB: Adenosine** should be **avoided** as blocking the AV node can paradoxically increase ventricular rate resulting in fall in cardiac output.

**NB: Verapamil** and **digoxin** should also be **avoided** in patients with Wolff-Parkinson White as they may precipitate VT or VF.

**NB**: D.D **Tall R in V1**:
- WPWS type A,
- RBBB,
- Posterior MI,
- Dressler's syndrome post MI and
- Dextrocardia.

# Atrial fibrillation (AF)

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia.
It is very common, being present in around 5% of patients over aged 70-75 years and 10% of patients aged 80-85 years.
Whilst uncontrolled atrial fibrillation can result in symptomatic palpitations and inefficient cardiac function probably the most important aspect of managing patients with AF is reducing the increased risk of stroke which is present in these patients.

## Classification

NICE updated their guidelines on the management of atrial fibrillation (AF) in **2021**.

### AF classified into 3 patterns:

1) **First detected episode** (irrespective of whether it is symptomatic or self-terminating).
2) **Recurrent** episodes, when a patient has 2 or more episodes of AF. If episodes of AF **terminate spontaneously** then the term **paroxysmal AF** is used. Such episodes **last less than 7 days (typically < 24 hours).** If the arrhythmia is not self-terminating then the term **persistent AF** is used. Such episodes usually **last greater than 7 days.**
3) **In permanent AF** there is continuous atrial fibrillation **which cannot be cardioverted or if attempts to do so are deemed inappropriate.** Treatment goals are therefore **rate control and anticoagulation** if appropriate.

## Symptoms and signs

### Symptoms

- palpitations
- dyspnoea
- chest pain

### Signs

- an irregularly irregular pulse

## Investigations

An ECG is essential to make the diagnosis as other conditions can give an irregular pulse, such as ventricular ectopics or sinus arrhythmia.

## Management

There are two key parts of managing patients with AF:

- Rate/rhythm control
- Reducing stroke risk

## Rate vs. rhythm control

There are two main strategies employed in dealing with the arrhythmia element of atrial fibrillation:

- **rate control**: accept that the pulse will be irregular, but slow the rate down to avoid negative effects on cardiac function
- **rhythm control**: try to get the patient back into, and maintain, normal sinus rhythm. This is termed cardioversion. Drugs (pharmacological cardioversion) and synchronised DC electrical shocks (electrical cardioversion) may be used for this purpose

For many years the predominant approach was to try and maintain a patient in sinus rhythm. This approach changed in the early 2000's and now the majority of patients are managed with a rate control strategy. NICE advocate using a rate control strategy except in a number of specific situations such as coexistent heart failure, first onset AF or where there is an obvious reversible cause.

## Rate control

A **beta-blocker** or a **rate-limiting calcium channel blocker** (e.g. diltiazem) is used first-line to control the rate in AF.

If one drug does not control the rate adequately NICE recommend combination therapy with any 2 of the following:

- a betablocker
- diltiazem
- digoxin

## Rhythm control

As mentioned above there are a subgroup of patients for whom a rhythm control strategy should be tried first. Other patients may have had a rate control strategy initially but switch to rhythm control if symptoms/heart rate fails to settle.

When considering cardioversion it is very important to remember that the moment a patient switches from AF to sinus rhythm presents the highest risk for embolism leading to stroke. Imagine the thrombus formed in the fibrillating atrium suddenly being pushed out when sinus rhythm is restored. For this reason patients must either have had a short duration of symptoms (less than 48 hours) or be anticoagulated for a period of time prior to attempting cardioversion.

### Reducing stroke risk

Some patients with AF are at a very low risk of stroke whilst others are at a very significant risk. Clinicians use risk stratifying tools such as the $CHA_2DS_2$-VASc score to determine the most appropriate anticoagulation strategy.

## Atrial fibrillation: anticoagulation

### Does the patient need anticoagulation?

The need for anticoagulation should be considered in patients with any history of AF, not just if they are in AF currently, i.e., the following groups should be assessed:

- symptomatic or asymptomatic **paroxysmal**, persistent or permanent atrial fibrillation
- atrial flutter
- a continuing risk of arrhythmia recurrence after cardioversion back to sinus rhythm or catheter ablation

NICE suggest using the **$CHA_2DS_2$-VASc** score to determine the most appropriate anticoagulation strategy. This scoring system superseded the $CHADS_2$ score.

| | Risk factor | Points |
|---|---|---|
| **C** | Congestive heart failure | **1** |
| **H** | Hypertension (or treated hypertension) | **1** |
| **$A_2$** | Age >= 75 years | **2** |
| | Age 65-74 years | **1** |
| **D** | Diabetes | **1** |
| **$S_2$** | Prior Stroke, TIA or thromboembolism | **2** |
| **V** | Vascular disease (including ischaemic heart disease and peripheral arterial disease) | **1** |
| **S** | Sex (female) | **1** |

The table below shows a suggested **anticoagulation strategy based on the score**

| Score | Anticoagulation |
|---|---|
| **0** | No treatment |
| **1** | Males: Consider anticoagulation<br>Females: No treatment (this is because their score of 1 is only reached due to their gender) |
| **2 or more** | Offer anticoagulation |

Remember that if a $CHA_2DS_2$-VASc score suggests no need for anticoagulation it is important to ensure a transthoracic echocardiogram has been done to exclude valvular heart disease, which in combination with AF is an absolute indication for anticoagulation.

**NB**: However, the following are conditions that, if present, may trump the decision to **anticoagulate**:

- Valvular heart disease (Mitral Stenosis).
- Prior peripheral embolism.
- Intracardiac thrombus.

## Assessing bleeding risk:

NICE warn us **not to withhold anticoagulation solely on the grounds of age or risk falls.** NICE now recommend we formalize this risk assessment using the **ORBIT scoring system** in the new guidelines. Previously the HAS-BLED scoring system was recommended.

| Variable | Points |
|---|---|
| Hemoglobin <130 g/L for males and < 120 g/L for females, or hematocrit < 40% for males and < 36% for females | **2** |
| Age > 74 years | **1** |
| Bleeding history (GI bleeding, intracranial bleeding or hemorrhagic stroke) | **2** |
| Renal impairment (GFR < 60 mL/min/1.73m²) | **1** |
| Treatment with antiplatelet agents | **1** |

There are no formal rules on how we act on the ORBIT score and individual patient factors should be taken into account. However, the following table acts as a guide:

| ORBIT score | Risk group | Bleeds per 100 patient-years |
|---|---|---|
| 0-2 | Low | 2.4 |
| 3 | Medium | 4.7 |
| 4-7 | High | 8.1 |

### If treatment is indicated, which anticoagulant?

For many years warfarin was the anticoagulant of choice in atrial fibrillation. This changed following the development of **direct oral anticoagulants (DOACs).** These have the advantage of not requiring regular blood tests to check the INR and now recommended as the first-line anticoagulant for patients with AF. If a patient was previously started on warfarin, NICE recommend discussing switching to a DOAC during a routine follow-up appointment.

The following DOACs are recommended by NICE for reducing stroke risk in **AF:**

- apixaban
- dabigatran
- edoxaban
- rivaroxaban

Warfarin is now used second-line, in patients where a DOAC is contraindicated or not tolerated.

Aspirin is not recommended for reducing stroke risk in patients with AF.

### Tips:

**Paroxysmal AF (PAF):** the patient should be **warfarinised** as the patient is at significant risk of an embolic stroke.

Also for anti-arrhythmic like **beta blocker; Bisoprolol** (it is the treatment of choice if there are no contraindications as achieve rate control during the **PAF** episode, beneficial for BP control, for LV impairment, beneficial for IHD).

**Sotalol** though effective treatment for paroxysmal AF is potentially pro-arrhythmic (increases risk of torsades by prolonging QT) and does not cardiovert AF but can help to **maintain** sinus rhythm.

**Esmolol IV** is a short acting βB used in treatment of paroxysmal SVT.

**Flecainide IV** is a good **chemical cardioversion** agent especially with **PAF** related to **alcohol** excess, but it is **contraindicated** in patients with structural heart disease and at high risk of IHD. Also, it can be used in **atrial flutter.**

**Diltiazem** is rate limiting but is generally used in beta blocker intolerant patients.

**Amiodarone is the typical second line choice**, but is not the usual first line choice and should be reserved for refractory cases due to its wide side effects profile.

**Digoxin** has little value in Paroxysmal AF.

Compared to a person in sinus rhythm, a patient with **AF** has 5 folds increased risk of **stroke.** Stroke mortality is also higher than those without AF.

NICE guidelines recommend that: for **AF** patients with **TIA**:

**Do C.T brain:**

- In the absence of cerebral infarction or haemorrhage **>>>** anticoagulation therapy should begin as soon as possible.
- In the presence of ischaemic stroke **>>>** wait two weeks before start anticoagulation to avoid haemorrhagic transformation.

**NB**: Patient with AF then developed **blindness** >>> so extensive bilateral **occipital lobe infarction** as a result of emboli shower. Neuroimaging should be urgently performed to confirm the diagnosis. The pupillary response will be preserved in this case.

## Atrial fibrillation: post-stroke

### Recommendations include:

- following a stroke or TIA, warfarin or a direct thrombin or factor Xa inhibitor should be given as the anticoagulant of choice. Antiplatelets should only be given if needed for the treatment of other comorbidities
- in acute stroke patients, in the absence of haemorrhage, anticoagulation therapy should be commenced after 2 weeks. If imaging shows a very large cerebral infarction, then the initiation of anticoagulation should be delayed

## Atrial fibrillation: cardioversion

### Onset less than 48 hours:

If the AF is definitely of less than 48 hours onset patients should be heparinised and cardioverted using either:

- **Electrical** - 'DC cardioversion'
- **Pharmacology**:
  - **Amiodarone** if structural heart disease,
  - **Flecainide** in those without structural heart disease or IHD.

### Onset > 48 hours:

If the patient has been in AF for more than 48 hours then **anticoagulation** should be given for at least **3 weeks prior to cardioversion.** An alternative strategy is to perform a transoesophageal echo **(TOE)** to exclude a left atrial appendage **(LAA) thrombus.** If excluded patients may be **heparinised and cardioverted immediately.**

**Following electrical cardioversion** patients should be **anticoagulated for at least 4 weeks.** After this time **decisions** about anticoagulation should be taken on an **individual** basis depending on the risk of recurrence (CHADS score).

If there is a **high risk of cardioversion failure** (e.g., previous failure or AF recurrence) then it is recommended to have at least 4 weeks amiodarone or sotalol prior to electrical cardioversion.

If the patient is **haemodynamically compromised** due to **AF** whatever the cause >>> the emergency treatment is **DC cardioversion: 200 J ⇒ 360 J ⇒ 360 J**.

1. Following electrical cardioversion if AF is confirmed as being less than 48 hours duration then further anticoagulation is unnecessary.
2. Patients who have risk factors for ischaemic stroke should be put on lifelong oral anticoagulation.

### Adverse signs necessitating DC cardioversion are:

- **SBP ≤90 mmHg.**
- **Heart rate ≥200 bpm.**
- **Impaired consciousness (confusion).**
- **Chest pain.**
- **Heart failure.**

## Atrial fibrillation: rate control and maintenance of sinus rhythm

### Rate control

Rate control should be offered as the first-line treatment strategy for atrial fibrillation except in people:

- whose atrial fibrillation has a reversible cause
- who have heart failure thought to be primarily caused by atrial fibrillation
- with new-onset atrial fibrillation (< 48 hours)
- with atrial flutter whose condition is considered suitable for an ablation strategy to restore sinus rhythm
- for whom a rhythm-control strategy would be more suitable based on clinical judgement

## Rhythm control

### Agents used to maintain sinus rhythm in patients with a history of atrial fibrillation

- beta-blockers
- dronedarone: second-line in patients following cardioversion
- amiodarone: particularly if coexisting heart failure

## Catheter ablation:

NICE recommends the use of catheter ablation for those with AF who have not responded to or wish to avoid, antiarrhythmic medication.

### Technical aspects

- the aim is to ablate the faulty electrical pathways that are resulting in atrial fibrillation. This is typically due to aberrant electrical activity between the pulmonary veins and left atrium
- the procedure is performed percutaneously, typically via the groin
- both radiofrequency (uses heat generated from medium frequency alternating current) and cryotherapy can be used to ablate the tissue

### Anticoagulation

- should be used 4 weeks before and during the procedure
- it should be remembered that catheter ablation controls the rhythm but does not reduce the stroke risk, even if patients remain in sinus rhythm. Therefore, patients still require anticoagulation as per their $CHA_2DS_2$-VASc score
  - **if score = 0: 2 months anticoagulation recommended**
  - **if score > 1: long-term anticoagulation recommended**

### Outcome

- notable complications include
  - cardiac tamponade
  - stroke
  - pulmonary vein stenosis
- **success rate**
  - around 50% of patients experience an early recurrence (within 3 months) of AF that often resolves spontaneously
  - longer term, after 3 years, around 55% of patients who've had a single procedure remain in sinus rhythm. Of patients who've undergone multiple procedures around 80% are in sinus rhythm

## Medications

### Agents used to rate control in patients with AF:

- beta-blockers
  - a common contraindication for beta-blockers is asthma
- calcium channel blockers
- digoxin

- not considered first-line anymore as they are less effective at controlling the heart rate during exercise
- should only be considered if he person does no or very little physical exercise or other rate-limiting drug options are ruled out because of comorbidities
- may have a role if there is coexistent heart failure

| Factors favouring rate control | Factors favouring rhythm control |
|---|---|
| ➢ Older than 65 years.<br>➢ History of IHD. | ➢ whose atrial fibrillation has a reversible cause.<br>➢ who have heart failure thought to be primarily caused by atrial fibrillation.<br>➢ with new-onset atrial fibrillation (< 48 hours)<br>➢ with atrial flutter whose condition is considered suitable for an ablation strategy to restore sinus rhythm<br>➢ for whom a rhythm-control strategy would be more suitable based on clinical judgement |

Patients under 75 with mitral valve prolapse (MVP) who are in atrial fibrillation or those who have echocardiographic evidence ot left ventricular impairment should be referred for surgical assessment as arly as possible. A TOE (Transoesophageal Echocardiogram) can demonstrate whether the valve is amenable to repair or needs replacement. this is often performed intra-operatively Progressive mitral regurgitation is the most serious complication occurring in about 15% of patients over a 15-year period Acute hemiplegia, transient ischaemic attacks. cerebellar infarcts, amaurosis fugax and retinal arterioral Occlusions all oceur more frequently in MVP patients. suggesting that cereoral embali are actually quite Common in this condition

## Atrial fibrillation: pharmacological cardioversion

Agents with proven efficacy in the pharmacological cardioversion of atrial fibrillation

- **amiodarone**
- **flecainide** (if no structural heart disease)
- others (less commonly used in UK): quinidine, dofetilide, ibutilide, propafenone

### Less effective agents

- beta-blockers (including sotalol)
- calcium channel blockers
- digoxin
- disopyramide
- procainamide

## Atrial flutter

Atrial flutter is a form of supraventricular tachycardia characterised by a succession of rapid atrial depolarisation waves.

### ECG findings:

- 'sawtooth' appearance
- As the underlying **atrial rate is often around 300/min** the **ventricular or heart rate is dependent on the degree of AV block.** For example if there is **2:1 block the ventricular rate will be 150/min.**
- flutter waves may be visible following carotid sinus massage or adenosine

### Management:

- It is **similar to that of atrial fibrillation** although **medication** may be **less** effective.
- Atrial flutter is **more sensitive to cardioversion** however so **lower energy** levels may be used
- **Radiofrequency ablation of the tricuspid valve isthmus** is curative for most patients.

NB: Tachycardia with a rate of 150/min >>>>? Atrial flutter

## Multifocal atrial tachycardia (MAT)

Multifocal atrial tachycardia (MAT) may be defined as an **irregular** cardiac rhythm caused by **at least three different sites in the atria**, which may be demonstrated by **morphologically distinctive P waves.**
It is more common in **elderly** patients with chronic lung disease, for example **COPD**.

### Management:

- Correction of hypoxia and electrolyte disturbances.
- Rate-limiting CCBs are often used first-line **(Verapamil).**
- Cardioversion and digoxin are not useful in the management of MAT.

# Supraventricular tachycardia (SVT)

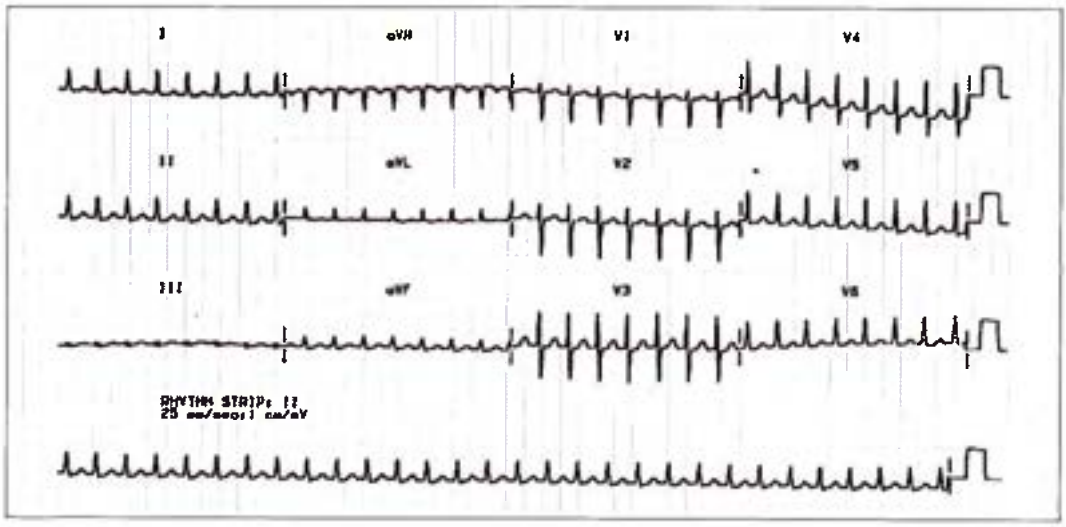
Whilst strictly speaking the term supraventricular tachycardia (SVT) refers to any tachycardia that is not ventricular in origin the term is generally used in the context of paroxysmal SVT.
Episodes are characterised by the **sudden onset** of a **narrow complex tachycardia,** typically an atrioventricular nodal re-entry tachycardia **(AVNRT).**

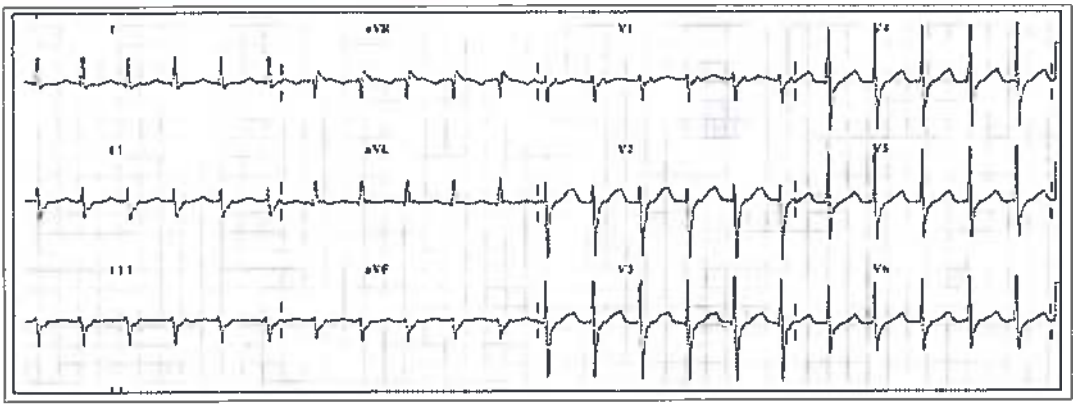
Other causes include atrioventricular re-entry tachycardias (AVRT) and junctional tachycardias.

AVNRT is often seen in young patients with no previous cardiac history. Potential triggers may include exercise, emotion, alcohol, use of stimulants such as caffeine. The re-entrant circuit is formed by the creation of 2 pathways, namely the slow and fast pathways.

The **fast** pathway is usually situated **anteriorly** along septal portion of tricuspid annulus.

The **slow** pathway is situated **posteriorly** close to the coronary sinus ostium.





## Acute management (by orders):

- **Vagal manoeuvres**: it is the **1st line** ttt in **stable** patient e.g. Carotid sinus massage, Valsalva manoeuvre, ice swallowing.
- **intravenous adenosine**
  - **rapid IV bolus of 6mg → if unsuccessful give 12 mg → if unsuccessful give further 18 mg**
- **DC-cardioversion** with very low energy **(50-100 J)**, the patient should be sedated before cardioversion.

Adenosine is contraindicated in asthmatics >> so, **verapamil IV** or **flecainide IV** is a preferable option

## Prevention of episodes:

- Beta-blockers
- Radio-frequency ablation

Regarding the termination of acute SVT in pregnancy, **adenosine** appears to be **safe** in **pregnancy**.

In the case of the prevention of recurrent SVT then verapamil or beta-blockers have data supporting their use.

Current AHA/EHA criteria for the treatment of SVTs in pregnancy do suggest using **metoprolol** (level of evidence 1B) rather than verapamil (C), although they recommend avoiding the former in the first trimester.

**EX: SVT with RBBB:**

An old male with past history of IHD, he had recurrent syncopal attacks, BP 110/70 mmHg and HR 170 bpm with no signs of LVF.

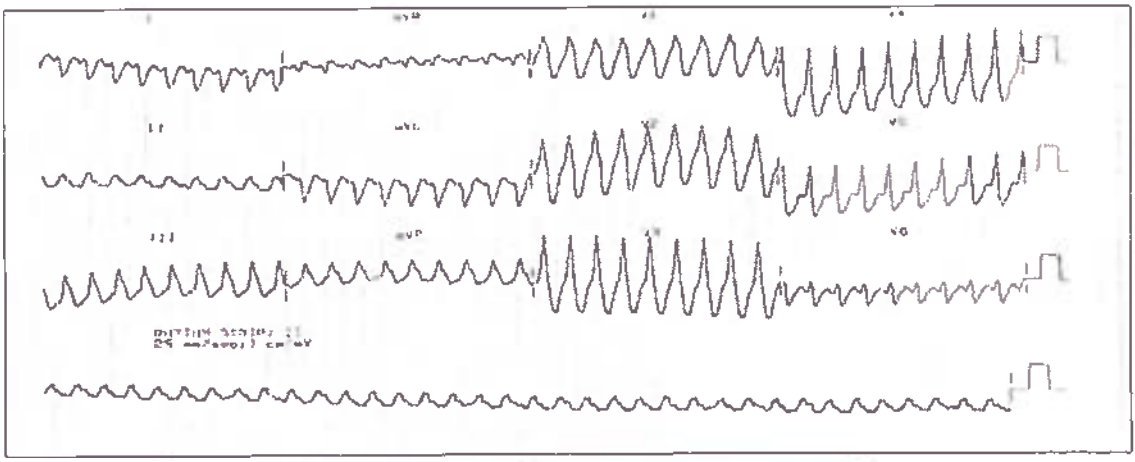
It is possible that he has been in RBBB for a significant period of time. It may be his syncopal presentation indicate a further episode of acute MI.

As he has preserved circulation so ventricular tachycardia is less likely.

Flecanide should not be used with a history of previous IHD.

Verapamil should be avoided as it can lead to a significant reduction in cardiac output.

**Synchronized DC cardioversion** is the most appropriate Treatment option here.



## Broad complex tachycardia

**Features suggesting VT rather than SVT with aberrant conduction:**

- **AV dissociation**
- Fusion or **capture beats**
- **QRS > 160 ms**
- **Positive QRS concordance in chest leads**
- **Marked left axis deviation**
- History of **IHD**
- **Lack** of response to **adenosine** or carotid sinus massage

# Pacemakers: temporary

## Indications for a temporary pacemaker:

- **Symptomatic** (haemodynamically unstable) **bradycardia**, not responding to atropine.
- **Post-ANTERIOR MI:**
  - **Complete heart block, or**
  - **Type II heart block.**
- **Trifascicular block prior to surgery.**

## Indications for permanent pacemaker:

- **Complete** heart block (3rd degree).
- **Type II second** degree HB even **asymptomatic.**
- **Symptomatic second** degree HB.
- Sinus **pause** of more than **3 seconds.**

**NB**: Post-INFERIOR MI complete heart block is common and can be managed conservatively if asymptomatic and haemodynamically stable.

**EX**: Pt after having a **permanent pacemaker** inserted by one month >> has **fever** and **back pain**. Why?? >> Due to **Staphylococci discitis** which are skin organisms most commonly introduced during pacemaker insertion and would present with back pain.

# Pacemaker nomenclature

Pacemakers are classified by the nature of their pacing mode using a code of up to **5** letters. The NBG Pacemaker code was developed by the North American Society of Pacing and Electrophysiology (**NASPE**) and the British Pacing and Electrophysiology Group (**BPEG**):

| 1st letter | 2nd letter | 3rd letter | 4th letter | 5th letter |
|---|---|---|---|---|
| The chamber being **paced** | The chamber being **sensed** | The **response** to sensing | **Rate modulation** | **Multi-site pacing** |
| **O**= None<br>**A**= Atrium<br>**V**= Ventricle<br>**D**= Dual (A+V)<br>**S**= Single (A or V) | **O**= None<br>**A**= Atrium<br>**V**= Ventricle<br>**D**= Dual (A+V)<br>**S**= Single (A or V) | **O**= None<br>**I**= Inhibited<br>**T**= Triggered<br>**D**= Dual (T+I) | **O** (or no letter) = None<br>**R**= Rate modulation | **O** (or no letter) = None<br>**A**= Atrium<br>**V**= Ventricle<br>**D**= Dual |

The **R** in this code stands for responsive, and in an otherwise fit and well 76-year-old, he should have a responsive element to his PPM (that is, increases his heart rate with exercise).

**EX**: A gentleman is 77-years-old and has a 9 second asystolic pause causing syncope. With no breakthrough ventricular activity >>> he should therefore have a dual chamber permanent pacemaker (**DDDR**).
**NB**: A biventricular pacemaker can be indicated in heart failure patients with reduced exercise capacity, and therefore is not warranted here.

## Brugada syndrome

Brugada syndrome is a form of inherited cardiovascular disease with may present with sudden cardiac death. It is inherited in an autosomal dominant fashion and has an estimated prevalence of 1:5,000-10,000. Brugada syndrome is more common in Asians.

### Pathophysiology

- a large number of variants exist
- around 20-40% of cases are caused by a **mutation in the SCN5A gene which encodes the myocardial sodium ion channel protein**

### ECG changes

- convex ST segment elevation > 2mm in > 1 of V1-V3 followed by a negative T wave
- partial right bundle branch block
- the ECG changes may be more apparent following the administration of flecainide or ajmaline - this is the investigation of choice in suspected cases of Brugada syndrome

### Management

- implantable cardioverter-defibrillator

ECG showing Brugada pattern, most marked in V1, which has an incomplete RBBB, a downsloping ST segment and an inverted T wave

## Catecholaminergic polymorphic ventricular tachycardia CPVT

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a form of inherited cardiac disease associated with sudden cardiac death. It is inherited in an autosomal dominant fashion and has a prevalence of around 1:10,000.

### Pathophysiology

- the most common cause is a defect in the ryanodine receptor (RYR2) which is found in the myocardial sarcoplasmic reticulum

### Features

- exercise or emotion induced polymorphic ventricular tachycardia resulting in syncope
- sudden cardiac death
- symptoms generally develop before the age of 20 years

### Management

- beta-blockers
- implantable cardioverter-defibrillator

## Implantable cardioverter defibrillators (ICD) (Dual chamber pacemaker)

### Indications:

- **Long QT syndrome (LQTS)**
- **Hypertrophic obstructive cardiomyopathy (HOCM)**
- **(ARVC) arrhythmogenic right ventricular cardiomyopathy causing cardiac arrest.**
- **Brugada syndrome**
- **Cardiac arrest due to VT/VF.**
- **Sustained VT causing haemodynamic compromise.**
- **Non-sustained VT on 24 hr. monitoring with prior MI.**
- **Unexplained syncope with VT inducible at EPS.**
- Inducible **VT on EPS** and **ejection fraction < 35%.**
- Chronic heart failure, left ventricular ejection fraction (LVEF) less than 40% and associated syncope episodes due to non-sustained VT post-MI, non- sustained VT with LVEF less than 40%.
- **Following repair of tetralogy of Fallot.**
- **SSS (sick sinus syndrome)**

**Patients with heart failure** are at increased risk of SCD from ventricular arrhythmias. So ICD is indicated for **primary prevention of SCD** in patients who have history of **prior MI** and **all of the following**:

- Non-sustained VT.
- Inducible arrhythmia on EPS.
- LV EF less than 35% and no worse than NYHA class III.

So that all these patients should be **evaluated by EPS** and **if inducible arrhythmias** are documented, an **ICD** should be placed.

Some trials like MADIT II have also found that ICD implantation in such patients even without EPS also leads to reduction in mortality, although guidelines are yet to completely reflect this information.

# Hypertension

## Hypertension: diagnosis and management

**NICE published updated guidelines for the management of hypertension, please refer to the guidelines 2019.**

- Classifying hypertension into stages.
- Recommending the use of **ambulatory blood pressure monitoring** (**ABPM**) and home blood pressure monitoring (HBPM).
- In the past there was overtreatment of **'white coat' hypertension**.
- The use of ambulatory blood pressure monitoring (ABPM) aims to reduce this. There is also good evidence that ABPM is a better predictor of cardiovascular risk than clinic blood pressure readings.
- Calcium channel blockers are now considered superior to thiazides.
- Bendroflumethiazide is no longer the thiazide of choice.

**The use of ambulatory blood pressure monitoring (ABPM) aims to:**

- prevent diagnosing 'white coat hypertension' as having hypertension in patients whose blood pressure climbs 20 mmHg whenever they enter a clinical setting.
- ABPM has been shown to be a more accurate predictor of cardiovascular events than clinic readings.

### Blood pressure classification:

This becomes relevant later in some of the management decisions that NICE advocate.

| Stage | Criteria |
|---|---|
| **Stage 1 hypertension** | Clinic BP >= 140/90 mmHg and subsequent ABPM daytime average or HBPM average BP >= 135/85 mmHg |
| **Stage 2 hypertension** | Clinic BP >= 160/100 mmHg and subsequent ABPM daytime average or HBPM average BP >= 150/95 mmHg |
| **Stage 3 or Severe hypertension** | Clinic systolic BP >= 180 mmHg, or clinic diastolic BP >= 120 mmHg |

### Diagnosing hypertension:

Firstly, NICE recommend measuring blood pressure in both arms when considering a diagnosis of hypertension.

- If the difference in readings between arms is more than 20 mmHg then the measurements should be repeated.
- If the difference remains > 20 mmHg then subsequent blood pressures should be recorded from the arm with the higher reading.
  It should of course be remember that

- there are pathological causes of unequal blood pressure readings from the arms, such as
  - supravalvular aortic stenosis.
  - listen to the heart sounds >> further investigation if a very large difference is noted.

**NICE also recommend**

- taking a second reading during the consultation, if the first reading is > 140/90 mmHg.
  - The lower reading of the two should determine further management.
- NICE suggest offering ABPM or HBPM to any patient with a blood pressure >= 140/90 mmHg.
- If the blood pressure is >= 180/120 mmHg:
- admit for specialist assessment if:
  - signs of retinal haemorrhage or papilloedema (accelerated hypertension) or
  - life-threatening symptoms such as new-onset confusion, chest pain, signs of heart failure, or acute kidney injury
- NICE also recommend referral if a phaeochromocytoma is suspected (labile or postural hypotension, headache, palpitations, pallor and diaphoresis)
- if none of the above then arrange urgent investigations for end-organ damage (e.g. bloods, urine ACR, ECG)
  - if target organ damage is identified, consider starting antihypertensive drug treatment immediately, without waiting for the results of ABPM or HBPM.
  - if no target organ damage is identified, repeat clinic blood pressure measurement within 7 days

**Ambulatory blood pressure monitoring (ABPM):**

- At least 2 measurements per hour during the person's usual waking hours (for example, between 08:00 and 22:00).
- Use the average value of at least 14 measurements.
- If ABPM is not tolerated or declined HBPM should be offered.

**Home blood pressure monitoring (HBPM):**

- For each BP recording, two consecutive measurements need to be taken, at least 1 minute apart and with the person seated.
- BP should be recorded **twice daily**, ideally in the morning and evening.
- BP should be recorded for **at least 4 days**, **ideally for 7 days.**
- Discard the measurements taken on the first day and use the **average** value of all the remaining measurements.

## Interpreting the results

**ABPM/HBPM >= 135/85 mmHg (i.e. stage 1 hypertension)**

- treat if < 80 years of age AND any of the following apply;
  - target organ damage,
  - established cardiovascular disease,
  - renal disease,
  - diabetes or a
  - 10-year cardiovascular risk equivalent to 10% or greater
- in 2019, NICE made a further recommendation, suggesting that we should 'consider antihypertensive drug treatment in addition to lifestyle advice for adults aged under 60 with stage 1 hypertension and an estimated 10-year risk below 10%. '.
- This seems to be due to evidence that QRISK may underestimate the lifetime probability of developing cardiovascular disease

**ABPM/HBPM >= 150/95 mmHg (i.e. stage 2 hypertension)**

- offer drug treatment regardless of age

## Managing hypertension:

- Lifestyle advice should not be forgotten and is frequently tested in exams:
  - a low salt diet is recommended,
    - aiming for **less than 6g/day, ideally 3g/day**.
    - The average adult in the UK consumes around 8-12g/day of salt.
    - A recent BMJ paper* showed that lowering salt intake can have a significant effect on blood pressure. For example, reducing salt intake by 6g/day can lower systolic blood pressure by 10mmHg.
  - caffeine intake should be reduced.
- the other general bits of advice remain:
  - stop smoking
  - drink less alcohol
  - eat a balanced diet rich in fruit and vegetables
  - exercise more, lose weight

**ABPM/HBPM >= 135/85 mmHg (i.e. stage 1 hypertension)**

- treat if < 80 years of age AND any of the following apply; target organ damage, established cardiovascular disease, renal disease, diabetes or a 10-year cardiovascular risk equivalent to 10% or greater
- in 2019, NICE made a further recommendation, suggesting that we should *'consider antihypertensive drug treatment in addition to lifestyle advice for adults aged under 60 with stage 1 hypertension and an estimated 10-year risk below 10%. '*. This seems to be due to evidence that QRISK may underestimate the lifetime probability of developing cardiovascular disease

**ABPM/HBPM >= 150/95 mmHg (i.e. stage 2 hypertension)**

- offer drug treatment regardless of age

For patients < 40 years consider specialist referral to exclude secondary causes.

## Step 1 treatment:

- patients < 55-years-old or a background of type 2 diabetes mellitus: **A**CE inhibitor or a **A**ngiotensin receptor blocker (**A**CE-i or **A**RB): **(A)**
  - **angiotensin receptor blockers should be used where ACE inhibitors are not tolerated (e.g. due to a cough)**
- **patients >= 55-years-old** or of black African or African–Caribbean origin: **C**alcium channel blocker **(C)**
  - **ACE inhibitors have reduced efficacy in patients of black African or African–Caribbean origin are therefore not used first-line**

## Step 2 treatment:

- if already taking an **A**CE-i or **A**RB add a **C**alcium channel blocker or a thiazide-like **D**iuretic
- if already taking a **C**alcium channel blocker add an **A**CE-i or **A**RB or a thiazide-like **D**iuretic
  - for patients of black African or African–Caribbean origin taking a calcium channel blocker for hypertension, if they require a second agent consider an angiotensin receptor blocker in preference to an ACE inhibitor
- **(A + C) or (A + D) or (C + A) or (C + D)**

## Step 3 treatment:

- add a third drug to make, i.e.:
  - if already taking an **(A + C)** then add a **D**
  - if already **(A + D)** then add a **C**
- **(A + C + D)**

## Step 4 treatment:

- NICE define step 4 as resistant hypertension and suggest either adding a 4th drug (as below) or seeking specialist advice
- first, check for:
  - confirm elevated clinic BP with ABPM or HBPM
  - assess for postural hypotension.
  - discuss adherence
- Consider **further diuretic** treatment.
- If potassium < 4.5 mmol/l add **spironolactone 25mg OD.**
- If potassium > 4.5 mmol/l consider an **alpha- or beta-blocker**
- If BP still not controlled seek specialist advice.

Although polypharmacy is in general to be avoided, in a patient with recognised HTN **adding in a second drug is more effective than increasing doses of a first drug.**

Those **under 55 yrs**. old with HTN are advised to start on an **ACE inhibitor** at first (or **ARB blocker** should they be intolerant).

The starting dose of **Ramipril** is **1.25 mg** rather than 10 mg, which is **up titrated** in the absence of hypotension depending on satisfactory renal function.

ACE inhibitors have reduced efficacy in **black** patients (**Afro-Caribbean origin**) they have lower renin levels and are therefore not used first-line, so you can use **CCB** e.g. **Amlodipine** but **if not tolerated** due to LL oedema, so can use **thiazide**, and if still high BP you can **use ARBs like Valsartan**.

**CCBs** are presently recommended as first-line treatment in those **over 55**, or all patients of **African or Caribbean descent**.

If a CCB is not suitable, for example because of oedema or intolerance, or if there is evidence of HF or a high risk of HF, offer a **thiazide** diuretic.

**NB:** BB is not recommended as a 1st or 2nd line anti-hypertensive agent, particularly in obese population because of its association with **impaired glucose tolerance.**

The NICE guidelines on HTN advise **against** using **beta-blockers** as **routine 'first** line' therapy for **uncomplicated** hypertension.

Review of several randomised controlled trials suggested that first line beta-blockers were not as good at decreasing mortality as other classes of antihypertensive drugs and were less well tolerated.

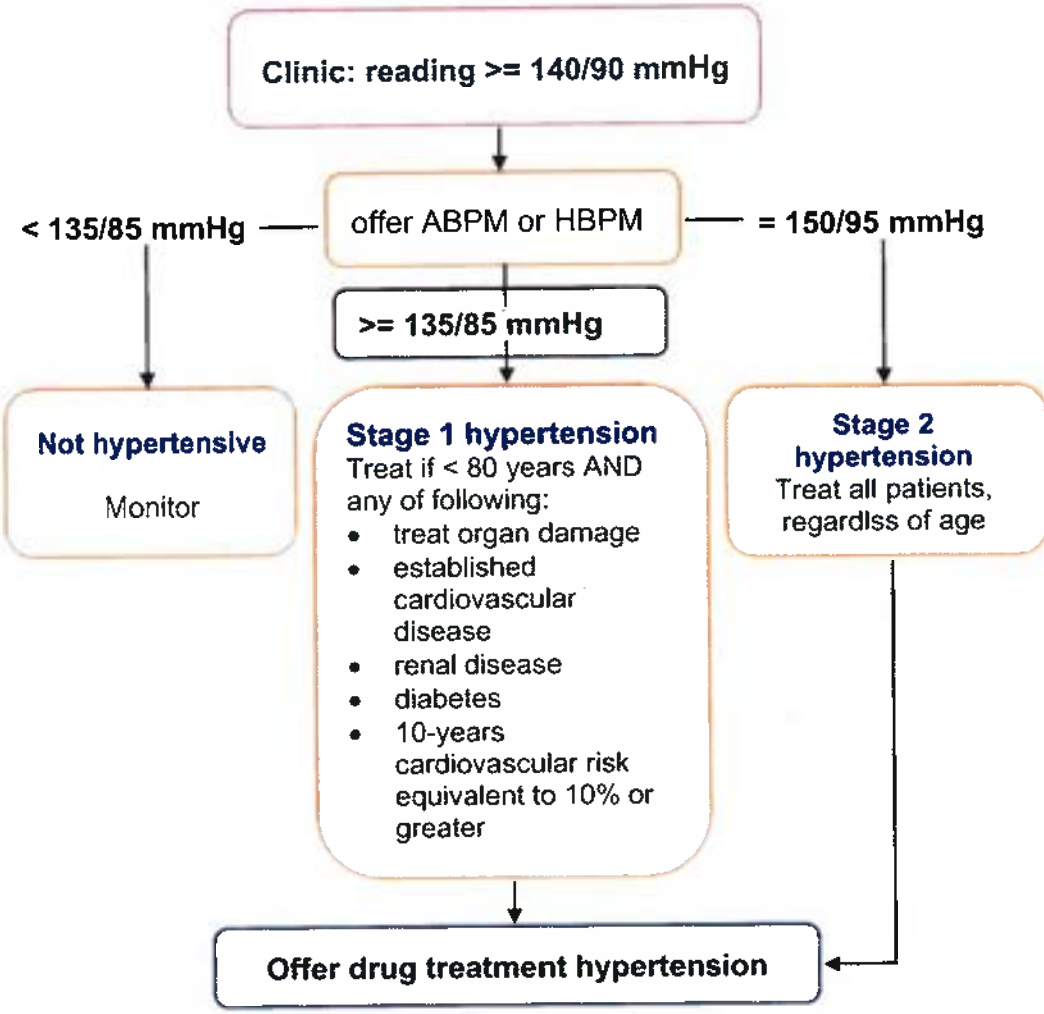
## Blood pressure targets:

| | Clinic BP | ABPM / HBPM |
|---|---|---|
| Age < 80 years | 140/90 mmHg | **135/85** mmHg |
| Age > 80 years | 150/90 mmHg | **145/85** mmHg |

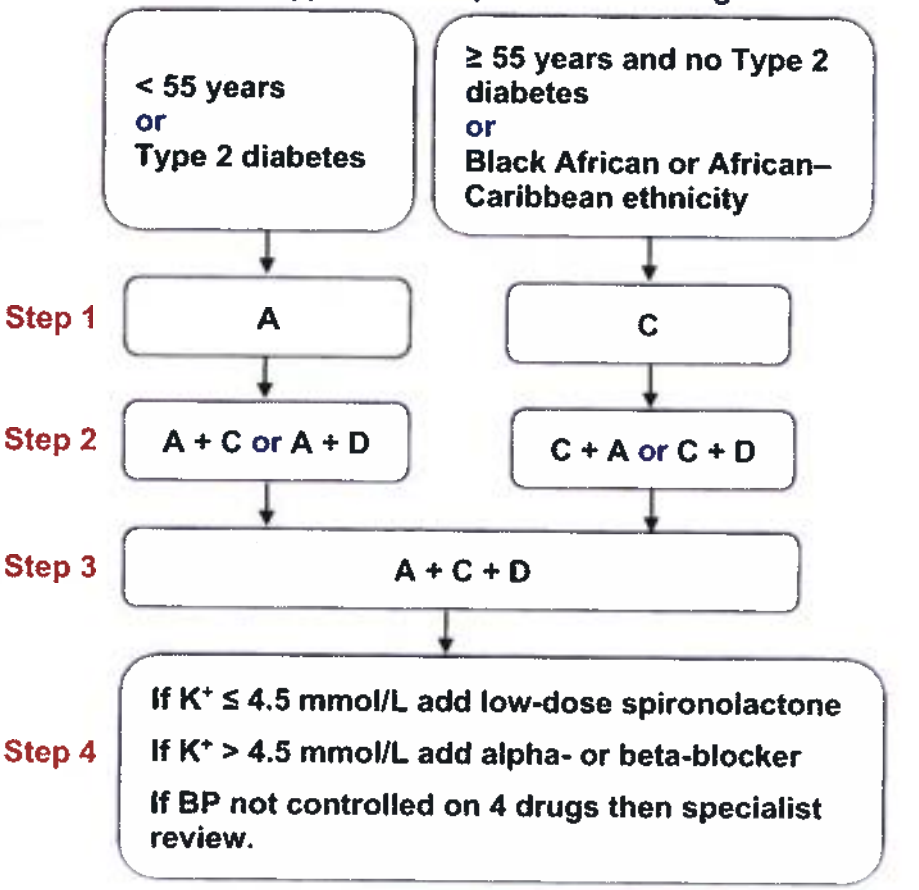
Goal BP **less than 130/85 mmHg** for patients with DM, CKD and established CVD like IHD. (**BHS**).

While in non-diabetic patients with CVD, the target BP is **less than 140/90 mmHg.** (**JN C**) and (**ACC/AHA**).

## Summary of hypertension management


Clinic: reading >= 140/90 mmHg
offer ABPM or HBPM
< 135/85 mmHg
= 150/95 mmHg
>= 135/85 mmHg
Not hypertensive
Monitor
Stage 1 hypertension
Treat if < 80 years AND any of following:
• treat organ damage
• established cardiovascular disease
• renal disease
• diabetes
• 10-years cardiovascular risk equivalent to 10% or greater
Stage 2 hypertension
Treat all patients, regardlss of age
Offer drug treatment hypertension

Management of hypertension per current nice guidelines


< 55 years
or
Type 2 diabetes
≥ 55 years and no Type 2 diabetes
or
Black African or African–Caribbean ethnicity
Step 1
A
C
Step 2
A + C or A + D
C + A or C + D
Step 3
A + C + D
Step 4
If K+ ≤ 4.5 mmol/L add low-dose spironolactone
If K+ > 4.5 mmol/L add alpha- or beta-blocker
If BP not controlled on 4 drugs then specialist review.
Key
A = ACE-inhibitor or Angiotensin 2 receptor blocker
C = Calcium channel blocker
D = thiazide-like Diuretic

## Malignant hypertension

### Basics:

- Severe hypertension **(e.g. >200/130 mmHg)**.
- Occurs in both essential and secondary types.
- Fibrinoid necrosis of blood vessels, leading to retinal haemorrhages, exudates, and proteinuria, haematuria due to renal damage (benign nephrosclerosis).
- Can lead to cerebral oedema → encephalopathy.

### Features:

- Classically: severe headaches, nausea/vomiting, visual disturbance
- However chest pain and dyspnoea common presenting symptoms
- Papilledema
- Severe: encephalopathy (e.g. seizures)

### Management:

- Reduce **diastolic** but **no lower than 100mmHg within 12-24 hrs**
- Bed rest
- Most patients: oral therapy e.g. atenolol
- If severe/encephalopathy: **IV sodium nitroprusside / labetalol**

According to NICE guidelines, you should **refer patients to specialist care** the same day if they have:

- **Accelerated hypertension** (BP usually higher than **180/110** mmHg with signs of **papilledema** and/or **retinal haemorrhage**), or
- **Suspected phaeochromocytoma** (labile or postural hypotension, headache, palpitations, pallor and diaphoresis).

## Hypertensive crisis

### Hypertensive crisis:

- Hypertensive emergency >> systolic BP ≥ 180 or diastolic BP ≥ 110 + end organ damage
- Hypertensive urgency >> systolic BP ≥ 180 or diastolic BP ≥ 110 + **NO** end organ damage

**The most common clinical presentations of hypertensive emergencies are:**

- **cerebral infarction** (24.5%),
- pulmonary edema (22.5%),

- hypertensive encephalopathy (16.3%),
- congestive heart failure (12%).
- Other presentations include intracranial hemorrhage, aortic dissection, and eclampsia as well as acute myocardial infarction.
- (NICE) recommends **same day referral for:**
  - **accelerated hypertension with papilloedema and/or retinal haemorrhages,** or
  - for patients suspected of having a phaeochromocytoma (labile or postural hypotension, headache, palpitations, pallor and sweating).

**Hypertensive emergency:**

- **The initial target is to lower the mean arterial pressure (MAP) by no more than 25%, or reduce the diastolic blood pressure by one-third**
- (MAP) = diastolic blood pressure + [(systolic blood pressure - diastolic blood pressure)/3]
  - Or MAP = (2x diastolic + systolic)/3
- Even in the presence of heart failure or hypertensive encephalopathy, a controlled reduction, to a level of about 150/90 mmHg, over a period of 24-36 hours is ideal
- In most patients, blood pressure can be brought down with bed rest and oral medication
- Intravenous labetalol (2 mg/min to a maximum of 200 mg), intravenous glyceryl trinitrate (0.6-1.2 mg/h), intravenous sodium nitroprusside (0.3-1.0 mg/kg per min) and intramuscular hydralazine (5 or 10 mg repeated at half-hourly intervals) are all effective but require close monitoring
  - **Labetalol has both alpha- and beta-adrenoreceptor antagonistic activity and is the first choice for hypertensive crises where the aetiology is initially unclear.**

## Hypertension: secondary causes

It is thought that between 5-10% of patients diagnosed with hypertension have **primary hyperaldosteronism**, including Conn's syndrome. This makes it the single most common cause of secondary hypertension.

**Renal** - accounts for **80%** of secondary hypertension:

- Glomerulonephritis
- Pyelonephritis
- Adult polycystic kidney disease
- Renal artery stenosis

### Endocrine disorders:

- **Cushing's** syndrome
- **Conn's** syndrome (Primary hyperaldosteronism)
- **Liddle's** syndrome
- **Congenital adrenal hyperplasia (11-beta hydroxylase deficiency)**
- **Phaeochromocytoma**
- **Acromegaly**

### Drug causes:

- Combined oral contraceptive pill
- Steroids
- NSAIDs
- MAO
- l leflunomide

### Other causes include:

- Coarctation of the aorta
- Pregnancy

## Isolated systolic hypertension (ISH):

- ISH is common in the elderly, affecting around **50%** of people **older than 70 years old**.
- ISH (systolic BP **>160** and diastolic BP **<90** mmHg).
- It is associated with a **greater risk than combined** systolic/diastolic hypertension.
- The Systolic Hypertension in the Elderly Program (SHEP) back in 1991 established that treating ISH reduced both strokes and IHDs.
- **The NICE guidelines** recommended **treating isolated systolic hypertension the same way as standard hypertension.** (Previously thiazides were recommended as first line agents)

## hypertension management IN Diabetes mellitus:

Hypertension is an added cardiovascular risk factor for diabetics and should therefore by actively looked for and treated.

It is also a risk factor for the development of diabetic nephropathy.

### Selected points:

- The blood pressure target for diabetics is **140/80 mmHg, but.**
- If there is end-organ damage the target is **130/80 mmHg.**
- **ACEIs** are **first-line regardless of age.**

- Otherwise managed according to standard NICE guidelines.
- Avoid the routine use of beta-blockers in uncomplicated hypertension, particularly when given in combination with thiazides, as they may cause insulin resistance, impair insulin secretion and alter the autonomic response to hypoglycaemia.
- Remember that autonomic neuropathy may result in more postural symptoms in patients taking antihypertensive therapy.

## Hypertension in pregnancy

Women who are at high risk of developing pre-eclampsia should **take aspirin 75mg OD from 12 weeks until the birth of the baby.**

### High risk groups include:

- Hypertensive disease during previous pregnancies
- Type 1 or 2 diabetes mellitus
- Chronic kidney disease
- Autoimmune disorders such as SLE or Antiphospholipid syndrome

The classification of hypertension in pregnancy is complicated and varies.

### Remember, in normal pregnancy:

- **Blood pressure** usually **falls in the first trimester** (particularly the **diastolic**), and **continues to fall until 20-24 weeks.**
- **After this time** the blood pressure **usually increases to pre-pregnancy levels by term.**
- The **heart rate increases** by 10-20 bpm, **stroke volume** and **cardiac output increase** but **venous pressure should remain** the same due to a 25% reduction in systemic and pulmonary vascular resistance.

Blood pressure during pregnancy normally falls in first half of pregnancy before rising to pre-pregnancy levels before term.

### Hypertension in pregnancy in usually defined as:

- **Systolic > 140 mmHg** or **diastolic > 90 mmHg.**
- **Or** an increase above usual office readings of **> 30 mmHg systolic** or **> 15 mmHg diastolic.**

NB: The **target BP** in patients with **pre-existing hypertension** is 140/90 mmHg.

As in patients with longstanding HTN aggressive BP control may compromise placental function, so **diastolic blood pressure should be preserved > 80 mmHg.** Any increase in BP above baseline should prompt a search for new pre-eclampsia

**After establishing that the pregnant lady is hypertensive, she should be categorised into one of the following groups:**

| Pre-existing hypertension (Chronic HTN) | Pregnancy-induced hypertension (PIH), (Gestational hypertension) | Pre-eclampsia |
|---|---|---|
| ➢ A history of hypertension **before pregnancy** or an elevated blood pressure > 140/90 mmHg **before 20 weeks gestation.**<br>➢ **No** proteinuria, **No** oedema.<br><br>Occurs in 3-5% of pregnancies and is more common in older women. | ➢ Hypertension (as defined above) occurring in the second half of pregnancy (i.e. **after 20 Wks**).<br>➢ **No** proteinuria, **No** oedema<br>➢ Occurs in around 5-7% of pregnancies.<br>➢ Resolves following birth (typically after one month).<br>➢ Women with PIH are at increased risk of future pre-eclampsia or HTN later in life. | ➢ Pregnancy-induced hypertension after 20 wks. in association with **proteinuria** (>0.3g / 24 hours)<br>➢ **Oedema** may occur but is now less commonly used as a criteria.<br><br>Occurs in around **5%** of pregnancies. |

**NB:** The raised ambulatory blood pressure readings exclude a diagnosis of white-coat hypertension.

## Pre-eclampsia

Pre-eclampsia describes the emergence of high blood pressure during pregnancy that may be a precursor to a woman developing eclampsia and other complications. It is classically a triad of 3 things:

- new-onset hypertension
- proteinuria
- oedema

### Definition

#### The current formal definition is as follows

- new-onset blood pressure ≥ 140/90 mmHg after 20 weeks of pregnancy, AND 1 or more of the following:
  - proteinuria
  - other organ involvement (see list below for examples): e.g. renal insufficiency (creatinine ≥ 90 umol/L), liver, neurological, haematological, uteroplacental dysfunction

## Features

### Potential consequences of pre-eclampsia

- eclampsia
  - other neurological complications include altered mental status, blindness, stroke, clonus, severe headaches or persistent visual scotomata
- fetal complications
  - intrauterine growth retardation
  - prematurity
- liver involvement (elevated transaminases)
- haemorrhage: placental abruption, intra-abdominal, intra-cerebral
- cardiac failure

## Risk factors:

- **> 40 years old**
- **Null parity (or new partner)**
- **Multiple pregnancy (twins)**
- **Pregnancy interval of more than 10 years**
- **BMI > 30 kg/m^2**
- **DM**
- **Family history of pre-eclampsia**
- **Previous history of pre-eclampsia**
- **Pre-existing vascular disease such as hypertension or renal disease.**

## Features of severe pre-eclampsia:

- **Hypertension**: typically > 160/110 mmHg and proteinuria as above
- **Proteinuria**: dipstick ++/+++
- **Headache**
- Visual disturbance, **Papilledema**
- **Hyperreflexia, clonus**
- **RUQ/epigastric pain**
- **HELLP syndrome**: **H**aemolysis, **E**levated **L**iver enzymes, **L**ow **P**latelet count < 100 * $10^6$/l.

Nearly 10% of women with severe preeclampsia and 30-50% of women with eclampsia are affected by HEELP syndrome.
The exact relationship between HELLP syndrome and Pre-eclampsia is unknown.

**One third** of women with **pre-eclampsia (HELLP)** develop **DIC** or **TTP**.

## Management:

**Pre-eclampsia >>> best and definitive Treatment is >>> Delivery of the baby.**

- Patients with chronic hypertension are at increased risk of developing pre-eclampsia and are therefore prescribed **75 mg of aspirin daily from 12 weeks,** which is believed to reduce the risk.
- Consensus guidelines recommend **treating blood pressure > 160/110 mmHg** although many clinicians have a lower threshold.
- **Oral / IV labetalol** is now **first-line** following the 2010 NICE guidelines.
- Nifedipine, or **hydralazine** can be used as alternatives after considering side-effect profiles for the woman, foetus and new-born baby.
- **Delivery of the baby** is the **most** important and **definitive** management step. The timing depends on the individual clinical scenario.
- **MgSo4** is used **peri-delivery** to reduce the risk of seizures, and may have adjunctive effects on lowering BP and would be considered as the potential next step after BP lowering by IV labetalol. **(Firstly Labetalol IVI then MgSo4 IVI).**

**EX:** Pregnant female 35 week with BP 180/130 mmHg, severe headache, blurring of vision, bilateral LL oedema, bilateral papilledema >>> Next step is **firstly IV labetalol, then MgSo4 IVI peri-delivery**.
**Labetalol oral** is **first** line for **moderate hypertension** in **pregnancy**, according to NICE guidance.

**Treatment of HTN in pregnancy:**
**Safe:**
- **Labetalol**,
- **Nifedipine**,
- **Aldomet** (max dose 1 gm BID),
- **Hydralazine**

**Not safe:**
- ACEI / ARBs (risk of renal agenesis and subsequent fetal death) and
- Diuretics (↓ volume expansion associated during normal pregnancy) are absolutely contraindicated.
- Atenolol is associated with IUGR and so it is not the first choice beta blocker for use in pregnancy, in contrast Labetalol is not associated with IUGR.

### Treatment of hyperemesis BNF 80 (2020-2021):

- vomiting during pregnancy Nausea in the first trimester of pregnancy is generally mild and does not require drug therapy.
- On rare occasions if vomiting is severe, short-term treatment with an antihistamine, such as promethazine, may be required. Prochlorperazine or metoclopramide hydrochloride are alternatives.
- If symptoms do not settle in 24 to 48 hours, then specialist opinion should be sought.
- Hyperemesis gravidarum is a more serious condition, which requires regular antiemetic therapy, intravenous fluid and electrolyte replacement and sometimes nutritional support.
- Supplementation with thiamine, must be considered in order to reduce the risk of Wernicke's encephalopathy.

## Eclampsia

**Eclampsia** is the development of **seizures** in association **pre-eclampsia**.

In eclampsia >>> Give magnesium sulphate first-line

**Magnesium sulphate** is used to both prevent seizures in patients with severe pre-eclampsia and treat seizures once they develop. Guidelines on its use suggest the following:

- should be given once a decision to deliver has been made
- in eclampsia an IV bolus of 4g over 5-10 minutes should be given followed by an infusion of 1g / hour
- **urine output, reflexes, respiratory rate and oxygen saturations** should be monitored during treatment
  - respiratory depression can occur: calcium gluconate is the first-line treatment for magnesium sulphate induced respiratory depression
- treatment should continue for 24 hours after last seizure or delivery (around 40% of seizures occur post-partum)

Other important aspects of treating severe pre-eclampsia/eclampsia include **fluid restriction** to avoid the potentially serious consequences of fluid overload.

### NICE guidelines (2019):

- Offer placental growth factor (PlGF)-based testing to help rule out pre-eclampsia in women presenting with suspected pre-eclampsia (for example, with gestational hypertension) between 20 weeks and up to

35 weeks of pregnancy. (See the NICE diagnostics guidance on PlGF-based testing to help diagnose suspected pre-eclampsia.)

- Consider labetalol to treat gestational hypertension.
- Consider nifedipine for women in whom labetalol is not suitable, and methyldopa if labetalol or nifedipine are not suitable.
- Base the choice on side-effect profiles, risk (including fetal effects) and the woman's preferences.
- Do not offer bed rest in hospital as a treatment for gestational hypertension.
- **find out why the committee made the 2019 recommendations on the monitoring and treatment of gestational hypertension and how they might affect practice, see rationale and impact.**

**NB: PPCM (peri-partum cardiomyopathy)**

- Peripartum cardiomyopathy is a dilated cardiomyopathy of uncertain aetiology occurring in the last month of pregnancy or within 5 months after delivery.
- Symptoms are the same as those of cardiac failure in non-pregnant patients.
- In order to make the diagnosis there must be
  1) absence of any other cause *tor* the cardiac failure,
  2) absence of heart disease before the last month of pregnancy, and
  3) documented systolic dysfunction.
- Pre-eclampsia is an important differential and must be excluded.
- A history of visual disturbance, headache, abdominal pain and peripheral oedema along with hyperretlexia, clonus, right-upper-quadrant tenderness, renal impairment and proteinuria all suggest pre-eclampsia.
- Treatment is the same as for the non-pregnant patient with cardiac failure, although angiotensin-converting enzyme inhibitors should be avoided. Ihe mainstay of medical treatment is digoxin and loop diuretics. If indicated nitrates and inotropic support with dobutamine should be used.

# Heart failure

## Heart failure

### Heart failure: NYHA classification (The New York Heart Association)

NYHA classification 1928 is widely used to classify the severity of heart failure:

**NYHA Class I:**

- **No symptoms**
- **No limitation:** ordinary physical exercise does not cause undue fatigue, dyspnoea or palpitations

**NYHA Class II:**

- Mild symptoms
- Slight limitation of physical activity: comfortable at rest but **ordinary activity** results in fatigue, palpitations or dyspnoea

**NYHA Class III:**

- Moderate symptoms
- Marked limitation of physical activity: comfortable at rest but **less than ordinary activity** results in symptoms

**NYHA Class IV:**

- Severe symptoms
- Unable to carry out any physical activity without discomfort: symptoms of heart failure are present even **at rest** with increased discomfort with **any** physical activity.

### Types:

Heart failure may be defined as a clinical syndrome where the heart is unable to pump enough blood to meet the metabolic needs of the body. It is usually a result of structural or functional heart disease, but the term is also sometimes used more broadly e.g. high-output heart failure, see below for more details.

There are multiple ways in which it can be classified.

**By ejection fraction**

Patients with heart failure may have a normal or abnormal left ventricular ejection fraction (LVEF). This is measured using echocardiography and a reduced LVEF is typically defined as < 35 to 40%. This is termed heart failure with reduced ejection fraction **(HF-rEF)** and affects roughly 50% of people diagnosed with heart failure.

The remaining 50% of patients will have preserved LVEF on echocardiography and are termed heart failure with preserved ejection fraction **(HF-pEF).**

**This terminology has largely replaced the systolic vs diastolic heart failure classification.** Whilst the overlap is not perfect, HF-rEF patients typically have systolic dysfunction (impaired myocardial contraction during systole), whereas HF-pEF patients have diastolic dysfunction (impaired ventricular filling during diastole).

| Systolic dysfunction | Diastolic dysfunction |
|---|---|
| Ischemic heart disease<br>Dilated cardiomyopathy<br>Myocarditis<br>Arrhythmias | Hypertrophic obstructive cardiomyopathy<br>Restrictive cardiomyopathy<br>Cardiac tamponade<br>Constrictive pericarditis |

**It should be noted that many of the guidelines for the management of heart failure (such as NICE) give recommendations for HF-rEF patients and don't cover the management of HF-pEF patients.**

### By time

**Heart failure is** typically described as being acute or chronic. Acute heart failure typically refers to an acute exacerbation of chronic heart failure. The most urgent symptoms are often due to left ventricular failure, resulting in pulmonary oedema. This is one of the most common reasons for attendance to the Emergency Department.

### By left / right

**HF-rEF and HF-pEF** typically develop left-sided heart failure.
This may be due to increased left ventricular afterload (e.g. arterial hypertension or aortic stenosis) or increased left ventricular preload (e.g. aortic regurgitation resulting in backflow to the left ventricle).

**Right-sided heart failure is** caused by either increased right ventricular afterload (e.g. pulmonary hypertension) or increased right ventricular preload (e.g. tricuspid regurgitation).
These terms may also be used to describe the *consequences* of heart failure, i.e. the backward failure of output of either the left or right ventricle.

### Left ventricular failure typically results in:

- pulmonary oedema
  - dyspnoea
  - orthopnoea
  - paroxysmal nocturnal dyspnoea
  - bibasal fine crackles

### Right ventricular failure typically results in:

- peripheral oedema
  - ankle/sacral oedema
- raised jugular venous pressure

- hepatomegaly
- weight gain due to fluid retention
- anorexia ('cardiac cachexia')

## Other types:

### High-output heart failure:

High-output heart failure refers to a situation where a 'normal' heart is unable to pump enough blood to meet the metabolic needs of the body.

## Causes:

- anaemia
- arteriovenous malformation
- Paget's disease
- Pregnancy
- thyrotoxicosis
- thiamine deficiency (wet Beri-Beri)

## Investigations:

The choice of investigation is determined by **whether the patient has previously had a myocardial infarction (MI) or not.**

Previous MI >>>> arrange **echocardiogram** within 2 weeks.

No previous MI >>>> measure serum natriuretic peptides (**BNP**):

- If levels are 'high' arrange echocardiogram within 2 weeks.
- If levels are 'raised' arrange echocardiogram within 6 weeks.

# B-type natriuretic peptide (BNP)

**B-type** natriuretic peptide (BNP) is a **hormone** produced mainly by the **left ventricular** myocardium in response to **strain (volume overload).**

Whilst **heart failure** is the most obvious cause of raised BNP levels any cause of left ventricular dysfunction such as **myocardial ischaemia** or **valvular disease** may raise levels.

Raised levels may also be seen due to reduced **excretion** in patients with chronic kidney disease.

Factors which **reduce** BNP levels include **treatment** with ACEIs, ARBs and diuretics.

So, BNP has a **good negative predictive value** rather than positive predictive value (i.e. like D-Dimer in PE).

**Effects of BNP:**

- **Vasodilator**
- **↑ GFR and inhibit Na reabsorption >>> Diuretic** and **natriuretic**
- **Suppresses** both sympathetic tone and the renin-angiotensin-aldosterone system.

**Clinical uses of BNP:**

**Diagnosing** patients with **acute dyspnoea**:

- A **low** concentration of BNP **(< 100 pg/ml)** makes **a diagnosis of heart failure unlikely,** but **raised** levels should prompt **further** investigation to confirm the diagnosis.
- NICE currently recommends BNP as a helpful test **to rule out** a diagnosis of heart failure.

**Prognosis** in patients with chronic heart failure:

- Initial evidence suggests **BNP is an extremely useful marker of prognosis**

**Guiding** treatment in patients with chronic heart failure:

- Effective treatment lowers BNP levels

**Screening for cardiac dysfunction:**

- **Not** currently recommended for population screening.

| | BNP | NTproBNP |
|---|---|---|
| High levels | > 400 pg/ml (116 pmol/litre) | > 2000 pg/ml (236 pmol/litre) |
| Raised levels | 100-400 pg/ml (29-116 pmol/litre) | 400-2000 pg/ml (47-236 pmol/litre) |
| Normal levels | < 100 pg/ml (29 pmol/litre) | < 400 pg/ml (47 pmol/litre) |

## Factors which alter the BNP level:

| Increase BNP levels | Decrease BNP levels |
|---|---|
| Left ventricular hypertrophy<br>Ischaemia<br>Tachycardia<br>Right ventricular overload<br>Hypoxaemia (including PE)<br>**GFR** < 60 ml/min<br>Sepsis<br>**COPD**<br>**Diabetes**<br>Age > 70<br>Liver cirrhosis | • **Obesity**<br>• **Diuretics**<br>• ACE inhibitors<br>• ARBs<br>• Beta-blockers<br>• Aldosterone antagonists |

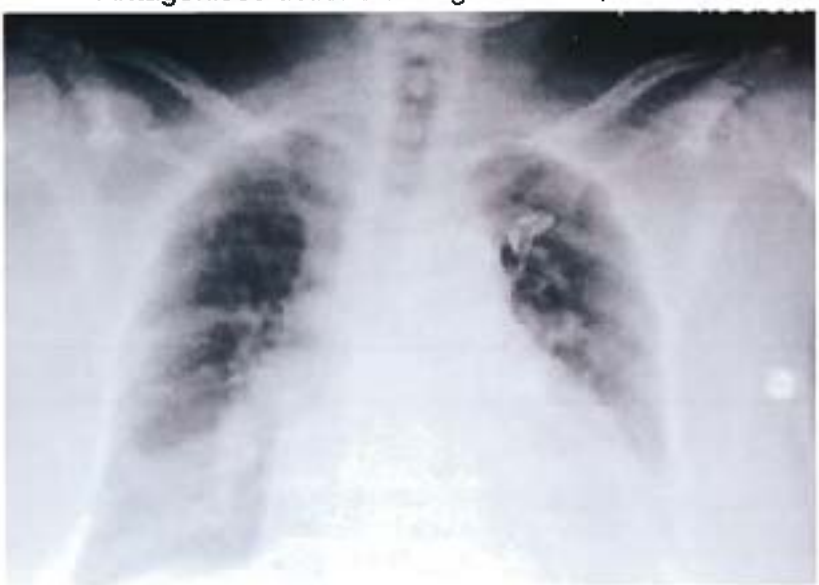
## Atrial natriuretic peptide (ANP)

**Basics:**

- Secreted mainly from **myocytes** of **right atrium** **and ventricle** in response to increased blood volme.
- Secreted by both the right and left **atria** (**right** >> left)
- 28 amino acid peptide hormone, which acts via cGMP
- **Degraded by endopeptidases**

**Actions:**

- Powerful **vasodilator**
- **Natriuretic**, i.e. promotes excretion of sodium
- Lowers BP
- Antagonises actions of angiotensin II, aldosterone



Cardiomegaly with pulmonary venous congestion and bilateral pleural effusions.

## Drug management in chronic heart faliure

NICE issued updated guidelines on management in 2018, key points are summarized here

Whilst loop diuretics play an important role in managing fluid overload it should be remembered that no long-term reduction in mortality has been demonstrated for loop diuretics such as furosemide.

## The first-line treatment for all patients is both an ACE-inhibitor and a beta-blocker

**NICE guidelines recommend the introduction of an ACE inhibitor prior to a beta-blocker in patients with chronic heart failure.**

Both **carvedilol** and **bisoprolol** have been shown to reduce mortality in stable heart failure. The other beta-blockers have no evidence base to support their use.

- generally, one drug should be started at a time. NICE advise that clinical judgement is used when determining which one to start first
- beta-blockers licensed to treat heart failure in the UK include bisoprolol, carvedilol, and nebivolol.
- ACE-inhibitors and beta-blockers have no effect on mortality in heart failure with *preserved* ejection fraction
- The **β blockers should be discontinued** in **acute fluid overload**

## Second-line treatment is an aldosterone antagonist

- these are sometimes referred to as mineralocorticoid receptor antagonists. Examples include spironolactone and eplerenone
- it should be remembered that both ACE inhibitors (which the patient is likely to already be on) and aldosterone antagonists both cause hyperkalaemia - therefore potassium should be monitored

**Third-line treatment should** be initiated by a specialist. Options include ivabradine, sacubitril-valsartan, hydralazine in combination with nitrate, digoxin and cardiac resynchronisation therapy

- **ivabradine**
  - criteria: sinus rhythm > 75/min and a left ventricular fraction < 35%
- **sacubitril-valsartan**
  - criteria: left ventricular fraction < 35%
  - is considered in heart failure with reduced ejection fraction who are symptomatic on ACE inhibitors or ARBs
  - should be initiated following ACEi or ARB wash-out period
- **digoxin**
  - digoxin has also not been proven to reduce mortality in patients with heart failure. It may however improve symptoms due to its inotropic properties
  - it is strongly indicated if there is coexistent atrial fibrillation
- **hydralazine in combination with nitrate**
  - this may be particularly indicated in Afro-Caribbean patients
- **cardiac resynchronisation therapy**
  - indications include a widened QRS (e.g. left bundle branch block) complex on ECG

## Other treatments:

- offer **annual influenza vaccine**
- offer one-off **pneumococcal vaccine**
  - adults usually require just one dose but those with asplenia, splenic dysfunction or chronic kidney disease need a booster every 5 years.

The RALES trial showed that spironolactone 25 mg daily reduced mortality by 30% when added to therapy of heart failure.
*Digoxin has also not been proven to reduce mortality in patients with heart failure. It may however improve symptoms due to its inotropic properties. Digoxin is strongly indicated if there is coexistent atrial fibrillation.

**EX:** A 62-year-old female is reviewed in the clinic despite current treatment with furosemide, bisoprolol, enalapril and spironolactone she remains breathless on minimal exertion and there is minimal ankle oedema, Echo: EF 35%. A combination of isosorbide dinitrate with hydralazine has been tried recently but had to be stopped due to side-effects. What additional medication would best help her symptoms? >>> **Digoxin / CRT.**
Digoxin may be useful in this situation whether the patient is in atrial fibrillation or not. Whilst it has not been shown to be of prognostic benefit it may help reduce symptoms. In the United States a large proportion of patients with heart failure take digoxin for this reason. Another option to consider in such a patient would be a CRT.

**CRT (Biventricular pacemaker implantation)** is recommended by NICE guidance for patients as long as they are currently experiencing or have recently experienced (NYHA) class III-IV symptoms:

1) They are in **sinus** rhythm with **wide QRS**:
   a. Either with a QRS duration of 150 ms or longer estimated by standard (ECG).
   b. Or with a QRS duration of 120-149 ms estimated by ECG and mechanical dyssynchrony that is confirmed by echocardiography.
2) They have a left ventricular ejection fraction **LVEF of 35%** or less.
3) They are receiving optimal **pharmacological** therapy.

## The following medications may exacerbate heart failure:

- **Pioglitazone** is contraindicated as it causes fluid retention.
- **Verapamil**: negative inotropic effect.
- **NSAIDs/glucocorticoids**: used with caution as they cause fluid retention.
- Class I antiarrhythmics; **Flecainide** (negative inotropic and proarrhythmic effect). Flecainide is contraindicated in patients with structural heart disease and IHD.

There are a number of biochemical parameters which provide useful prognostic information.

## Prognostic markers include: (2 High & 2 low)

- **High** BNP/NT-pro-BNP
- **↑ Uric acid**.
- **Anaemia**
- **Hyponatraemia**

**NB**: Non-iatrogenic hyponatraemia in CHF carries a poor prognosis. It was thought that specific **vasopressin antagonist** may offer a significant prognostic antagonist, but the data so far have proved very disappointing.

**NB**: Serum calcium is not a useful in prognosis in heart failure.cf5

# Aortic dissection

## Aortic dissection

The typical history of aortic dissection is sudden collapse with acute severe retrosternal central crushing chest pain within minutes radiating to the back in the presence of a recent normal exercise test (i.e. not IHD) and may be with history of chronic HTN.

### Pathophysiology

- tear in the tunica intima of the wall of the aorta

### Associations

**hypertension: the most important risk factor**

- trauma
- bicuspid aortic valve
- collagens: Marfan's syndrome, Ehlers-Danlos syndrome
- Turner's and Noonan's syndrome
- pregnancy
- syphilis

### Features:

- **chest/back pain**
  - typically severe and 'sharp', 'tearing' in nature
  - pain is typically maximal at onset
  - classically chest pain is more common in type A dissection and upper back pain is more common in type B dissection. However, there is considerable overlap and both chest and back pain are present in many patients
- **pulse deficit**
  - weak or absent carotid, brachial, or femoral pulse
  - variation (>20 mmHg) in systolic blood pressure between the arms
- **aortic regurgitation**
- **hypertension**
- **other features** may result from the involvement of specific arteries.
- **For example:**
  - coronary arteries → angina
  - spinal arteries → paraplegia
  - distal aorta → limb ischaemia
- **the majority of patients** have no or non-specific ECG changes. In a minority of patients, ST-segment elevation may be seen in the inferior leads

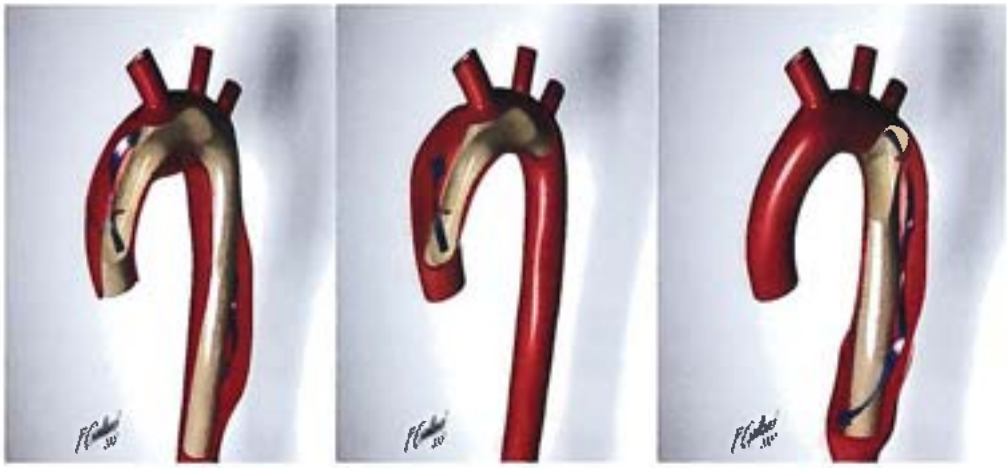
## Classification:

### Stanford classification:

- **Type A** - **Ascending** aorta, **2/3** of cases
- **Type B** - descending aorta, distal to left subclavian origin, 1/3 of cases

### DeBakey classification:

- **Type I** - originates in ascending aorta, propagates to at least the aortic arch and possibly beyond it distally
- **Type II** - originates in and is confined to the ascending aorta
- **Type III** - originates in descending aorta, rarely extends proximally but will extend distally



## Investigations:

It's important to remember that patients may present acutely and be clinically unstable. The choice of investigations will have to take account of this.

### Chest x-ray

- widened mediastinum

**CT angiography of the chest, abdomen and pelvis** is the investigation of choice

- suitable for stable patients and for planning surgery
- a false lumen is a key finding in diagnosing aortic dissection

### Transoesophageal echocardiography (TOE)

more suitable for unstable patients who are too risky to take to CT scanner

## Managment:

### Type A

- **Surgical** management, but **BP** should be controlled to a target systolic **SBP** of **100-120 mmHg** by **IV Labetalol, whilst awaiting intervention.**

### Type B

- Conservative management
- Bed rest
- Reduce blood pressure **IV labetalol** to prevent progression
- Endovascular repair of type B aortic dissection may have a role in the future.

## Complications

### Complications of backward tear:

- **Aortic regurgitation**
- **Inferior MI**: pattern often seen due to right coronary involvement
- **Cardiac tamponade**

### Complications of forward tear:

- **Unequal arm pulses and BP.**
- **Stroke.**
- **Renal failure.**

**Aortic dissection:**

- Type A - Ascending aorta - **control BP (IV labetalol) + surgery.**
- Type B - Descending aorta - **control BP (IV labetalol).**

**Beta blockers are the main** stay of medical therapy, as they are negative inotropic agent that will reduce the rate of left ventricular ejection and shear on the aortic wall.
The aim is to reduce **SBP to 100-120 mmHg** and the **HR to near 60 bpm**.

**Na nitroprusside** is a useful additional adjunct, it can be added if BP is not controlled by βB, but should **not** be used alone as it may increase rate of LV ejection.

Hydralazine should be avoided for the same reason.

If βB is unsuitable, then CCBs particularly non-dihydropyridines such as **diltiazem** would be a logical alternative.

Mortality for untreated aortic dissection is 25-30% at 24 hours and 65-70% at 2 weeks; dissections confined to the ascending aorta are associated with better survival (80%).

## NB: Features that favour oesophageal rupture over aortic dissection include:

- The history of onset while eating
- Blood pressure equal in both arms
- No diastolic murmur
- Good peripheral pulses
- Presence of a pleural effusion.

# Rheumatic fever

## Rheumatic fever

**Rheumatic fever develops following an immunological reaction to recent (2-6 weeks ago) *Streptococcus pyogenes* infection.**

### Pathogenesis:

- Streptococcus pyogenes infection → activation of the innate immune system leading to antigen presentation to T cells
- B and T cells produce IgG and IgM antibodies and CD4+ T cells are activated
- there is then a cross-reactive immune response (a form of type II hypersensitivity) thought to be mediated by molecular mimicry
- the cell wall of *Streptococcus pyogenes* includes M protein, a virulence factor that is highly antigenic. It is thought that the antibodies against M protein cross-react with myosin and the smooth muscle of arteries
- this response leads to the clinical features of rheumatic fever
- **Aschoff bodies** describes the granulomatous nodules found in rheumatic heart fever

### Diagnostic criteria:

Diagnosis is based on evidence of recent streptococcal infection accompanied by:

- **2 major** criteria
- **1 major** with 2 minor criteria

**Evidence of recent streptococcal infection**

- raised or rising streptococci antibodies,
- positive throat swab
- positive rapid group A streptococcal antigen test

**Major criteria**

- erythema marginatum
- Sydenham's chorea: this is often a late feature
- polyarthritis
- carditis and valvulitis (eg, pancarditis)
    - The latest iteration of the Jones criteria (published in 2015) state that rheumatic carditis cannot be based on pericarditis or myocarditis alone and that there must be evidence of endocarditis (the clinical correlate of which is valvulitis which manifests as a regurgitant murmur)
- subcutaneous nodules

### Minor criteria

- raised ESR or CRP
- pyrexia
- arthralgia (not if arthritis a major criteria)
- prolonged PR interval

## Management:

**Antibiotics:** oral penicillin V

- **anti-inflammatories**: NSAIDs are first-line
- treatment of any complications that develop e.g. heart failure

# Valvular heart diseases

## Aortic stenosis

- **Ejection systolic murmur** radiating to the carotid area and axilla.
- **Low Cardiac output symptoms** (chest pain, dyspnoea, syncope, episodes of pulmonary oedema etc.).
- **AS** may be asymptomatic.
- The classical symptoms are only in 30-40% of individuals with **AS**.
- When symptoms appear, survival without surgery is only average 2-3 years.
- SCD occurs in 1-2% of asymptomatic AS patients per year.

### Features of severe aortic stenosis:

- Narrow pulse pressure
- **Small volume pulse**
- **Slow rising pulse**
- **Delayed ESM**
- **Soft/absent S2**
- In severe AS >>> **reversed splitting of S2.**
- **S4**
- Thrill
- Duration of murmur
- **Left ventricular hypertrophy** or failure >>> **Displaced apex beat** (The apex beat is not normally displaced in aortic stenosis. Displacement would indicate left ventricular dilatation and hence severe disease).
- An overestimation of the severity of aortic stenosis can occur due to large volumes of blood passing over the valve at high velocities, which occurs in **aortic regurgitation.**

Aortic stenosis is associated with a worse prognosis when accompanied by left ventricular **(LV) dysfunction.**

Although the severity of valvular calcification is prognostically important in an asymptomatic patient **the most important predictor is LV function**.

## Causes of aortic stenosis:

- **Degenerative** calcification (most common cause in **older** patients > 65 years).
- **Bicuspid** aortic valve (most common cause in **younger** patients < 65 years).
- **Congenital: William's syndrome (supra-valvular aortic stenosis).**
- Post-**rheumatic** disease.
- Subvalvular: **HOCM.**

## Management:

- if asymptomatic then observe the patient is a general rule
- if **symptomatic then valve replacement**
- **if asymptomatic but valvular gradient > 40 mmHg** and with features such as left ventricular systolic dysfunction then consider surgery
- options for aortic valve replacement (AVR) include:
  - surgical AVR is the treatment of choice for young, low/medium operative risk patients. Cardiovascular disease may coexist. For this reason, an angiogram is often done prior to surgery so that the procedures can be combined
  - transcatheter AVR (TAVR) is used for patients with a high operative risk
- balloon valvuloplasty
  - may be used in children with no aortic valve calcification
  - in adults limited to patients with critical aortic stenosis who are not fit for valve replacement

AS >>> AVR if **symptomatic**, otherwise cut-off is gradient of 50 mmHg. Usually before valve replacement >>>do **coronary angiography**

The patient's **symptomatology** is probably the most important determinant in terms of the decision to operate for AVR.

A gradient of 50 mmHg would be regarded as moderate to severe AS but if asymptomatic nothing would be done.

LVH is a common feature of AS and does not influence the decision for surgery.

Calcific aortic disease is not of itself important and the gradient should be considered.

**NB:** Left ventricular systolic dysfunction/ failure >>>> will result in a decreased flow-rate across the aortic valve and hence a quieter murmur of AS.

**NB: ACEI is contraindicated in severe Aortic stenosis.**

**NB:** If patient has severe left ventricular (LV) dysfunction, and calculated valve area in such patients can be falsely low because low cardiac output reduces the valve opening forces. It is important to distinguish patients with true severe aortic stenosis (AS) with secondary LV dysfunction from those who have a falsely low calculated aortic valve area because of low cardiac output. An important method of distinguishing between the two conditions is to assess the haemodynamics after increasing the cardiac output by dobutamine infusion during echocardiography or cardiac catheterisation. Patients with truly severe AS manifest an increase in transaortic pressure gradient while the valve surface area remains the same during dobutamine infusion; while those with falsely low calculated valve area manifest an increase in calculated valve surface area. Dobutamine echocardiography is also important to assess LV contractile reserve. Patients who have 20%or more increase in stroke volume after dobutamine infusion have a much better prognosis after surgery compared to those who do not have LV contractile reserve.

**NB: Symptomatic AS+ small aortic valve area+ small PG** (less than 50 mmHg) + **low EF%** >>> should repeat **Echocardiography with dobutamine infusion**

**EX:** Pt with severe AS for AVR and also had LAD stenosis by 80% as revealed by coronary angiography >>> so management is AVR **PLUS** bypass grafting of the LAD using the left internal mammary artery **(LIMA).**

This patient has severe symptomatic aortic stenosis, which is an indication for aortic valve replacement. He also has LAD stenosis. As the patient is to have AVR, a concomitant bypass grafting of the LAD using the LIMA is the most appropriate option. The long-term patency of the LIMA is superior to that of a saphenous vein graft.
Percutaneous balloon aortic valvotomy is only used as a bridge to surgery in selected patients who are too sick to undergo AVR.

**Heyde's syndrome:**
It is a well-known association between **microcytic anaemia** and **calcific aortic stenosis.**

**Mechanism:** destruction of **vWF** as the platelets traverse the stenosed valve resulting in bleeding per rectum.

**The investigation of choice** after valve replacement is the **mesenteric angiography** as the bleeding vessels are poorly visualized on colonoscopy.

This would look for angiodysplasia, which may be associated with AS.

Resection of the diseased bowel has also been described as a treatment.

Haemodynamic optimisation prior to surgery with blood transfusion is preferred.

**Treatment: Aortic valve replacement,**

## Aortic regurgitation (AR)

Aortic regurgitation (AR) is the leaking of the aortic valve of the heart that causes blood to flow in the reverse direction during ventricular diastole.

It can be caused either by disease of the aortic valve or by distortion or dilation of the aortic root and ascending aorta.

### Features:

- **Wide pulse pressure** (with low DBP)
- Peripheral **vasoconstriction**, not dilatation, is typically found.
- **Collapsing pulse**
- Early **diastolic** murmur (a decrescendo murmur)
- **Austin-Flint murmur** in severe AR:
  - It is **mid/late diastolic murmur** which may show **pre-systolic accentuation** and is virtually indistinguishable from that of mitral stenosis.
  - It is due to partial closure of the anterior mitral valve cusps caused by the regurgitation streams.
  - There is **no correlation between** the presence of murmur and severity of AR, or aetiology.
  - The first heart sound S1 is normal but in severe cases it may be absent.

| Causes of AR due to valve disease | Causes of AR due to aortic root disease |
|---|---|
| • rheumatic fever: the most common cause in the developing world<br>• calcific valve disease<br>• infective endocarditis<br>• connective tissue diseases e.g. rheumatoid arthritis/SLE<br>• bicuspid aortic valve (affects both the valves and the aortic root) | • bicuspid aortic valve (affects both the valves and the aortic root)<br>• aortic dissection<br>• spondyloarthropathies (e.g. ankylosing spondylitis)<br>• hypertension<br>• syphilis<br>• Marfan's, Ehler-Danlos syndrome |

**NB:** Dilated cardiomyopathy >>> associated with MR not AR.

A 60-year-old man's echocardiogram shows a **dilated left ventricular (LV) cavity** with the remainder of the other chamber sizes normal >> **AR** as a **volume overload**. In AR would result in dilatation of the left ventricle.

But AS, HOCM and HTN would have the effect of causing **LV hypertrophy** and a smaller LV cavity.

### Management:

- medical management of any associated heart failure
- **surgery:** aortic valve indications include
- **Indications for AVR in severe AR (ACC/AHA):**
- All **symptomatic** patients with severe AR.
- **Asymptomatic** patients with severe AR if they have **depressed LV function (EF < 55%)** or
- **Asymptomatic** patients with severe AR if they have **severe LV dilatation (LVEDD >75 mm and LVESD > 55 mm).**

**NB**: Vasodilator therapy as **ACEI** or **CCB (Nifedipine)** ± **Thiazides** should be given to patients who do not have indications for AVR.

## Bicuspid aortic valve (BAV)

### Overview:

- It the **most common form** of **congenital** heart disease in **adults.**
- Occurs in **1-2%** of the population
- Usually **asymptomatic** in childhood

- It tends to be **sporadic** although there is a reported **familial** incidence of approximately **9%**.
- The majority eventually develop aortic stenosis or regurgitation
- Associated with:
  - A **left dominant coronary circulation** (the posterior descending artery arises from the circumflex instead of the RCA) and
  - **Turner's syndrome.**
- Around 5% of patients also have **coarctation of the aorta.**
- An **ejection click or sound**, best heard at the **apex**, implies that the site of the stenosis is mostly **valvular** and of **congenital** origin, that is, bicuspid valvular disease.

In a patient presenting with aortic stenosis (**AS**), what is the finding that would be most helpful in establishing a diagnosis of **congenital bicuspid valve** as the aetiology >>> An **ejection click or sound**, best heard at the **apex.**

### Complications:

- BAV have a propensity to wear out and calcify with ageing
- Aortic stenosis/regurgitation as above
- Higher risk for aortic dissection and aneurysm formation of the ascending aorta

### Treatment:

It is recorded that 1.2% per year incidence of **aortic valve replacement surgery** in individuals with BAV, although the vast majority occur in the fifth and sixth decades of life.

## Mitral stenosis

It is said that the causes of mitral stenosis are **rheumatic fever, rheumatic fever** and **rheumatic fever.**

Rarer causes that may be seen in the exam include mucopolysaccharidoses, carcinoid and endocardial fibroelastosis.

### Features:

- **Mid**-late **diastolic rumbling** murmur (best heard in expiration)
- **With pre-systolic** accentuation
- **Loud S1**
- **Opening snap**
- **Low volume pulse**
- **Malar flush**
- **Atrial fibrillation**

In particular MS is **poorly tolerated** in **pregnancy** due to **volume** overload.

## Features of severe MS:

- **Increases of length** of murmur
- **Opening snap** becomes **closer to S2**
- **Calcification** of the valve results in >>> **immobility** and **loss of the opening snap.**

## Chest x-ray

- left atrial enlargement may be seen

## Echocardiography:

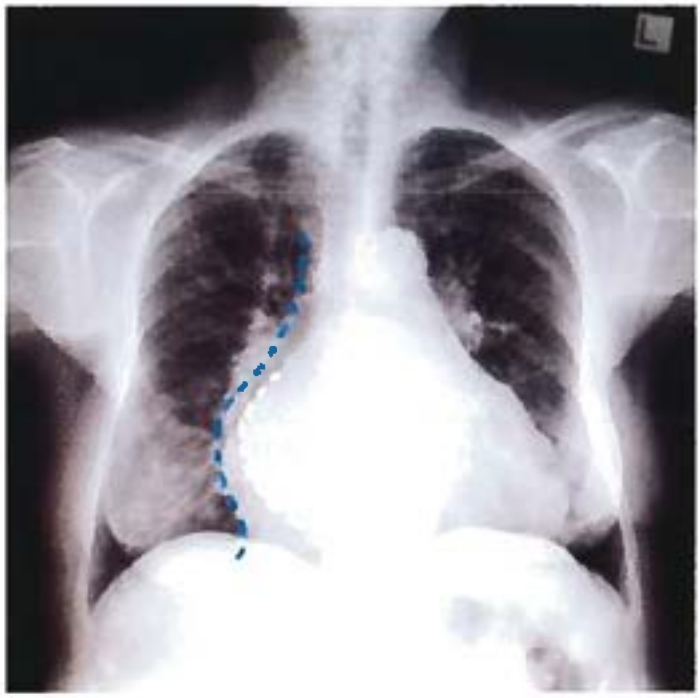
- **The normal cross sectional area of the mitral valve is 4-6 cm2.**
- A **'tight'** mitral stenosis implies a cross sectional area of **< 1 cm2.**

## Management:

- patients with associated atrial fibrillation require anticoagulation
  - currently warfarin is still recommended
- asymptomatic patients
  - monitored with regular echocardiograms
  - percutaneous/surgical management is generally not recommended
- symptomatic patients
  - percutaneous mitral balloon valvotomy
  - mitral valve surgery (commissurotomy, or valve replacement)

**Contraindications** for percutaneous mitral balloon valvotomy (= Indication of surgical mitral valve replacement):

- Moderate to **severe** MR.
- Heavily **calcified** mitral valve.
- LA thrombus.
- Concomitant coronary artery disease or other valve disease requiring surgery.



Chest x-ray from a patient with mitral stenosis. This patient has had a sternotomy and a prosthetic mitral valve. There is splaying of the carina with elevation of the left main bronchus, a double right heart border and cardiomegaly. The features are those of left atrial enlargement. Although the entire heart is enlarged, a double contour is seen through the right side of the heart. The more medial line is the enlarged left atrium (white dotted line) and the heart heart border is more lateral (blue dotted line).

## Mitral regurgitation (MR)

Also known as mitral insufficiency, mitral regurgitation (MR) occurs when blood leaks back through the mitral valve on systole. It is the second most common valve disease after aortic stenosis. The mitral valve is located between the left atrium and ventricle, and regurgitation leads to a less efficient heart as less blood is pumped through the body with each contraction. This said, MR is common in otherwise healthy patients to a trivial degree and does not need treatment.

As the degree of regurgitation becomes more severe, the body's oxygen demands may exceed what the heart can supply and as a result, the myocardium can thicken over time. While this may be benign initially, patients may find themselves increasingly fatigued as a thicker myometrium becomes less efficient, and eventually go into irreversible heart failure.

## Risk factors:

- Female sex
- Lower body mass
- Age
- Renal dysfunction
- Prior myocardial infarction
- Prior mitral stenosis or valve prolapse
- Collagen disorders e.g. Marfan's Syndrome and Ehlers-Danlos syndrome

## Causes:

- Following coronary artery disease or post-MI: if the papillary muscles or chordae tendinae are affected by a cardiac insult, mitral valve disease may ensue as a result of damage to its supporting structures.
- Mitral valve prolapse: Occurs when the leaflets of the mitral valve is deformed so the valve does not close properly and allows for backflow. Most patients with this have a trivial degree of mitral regurgitation.
- Infective endocarditis: When vegetations from the organisms colonising the heart grow on the mitral valve, it is prevented from closing properly. Patients with abnormal valves are more likely to develop endocarditis as opposed to their peers.
- Rheumatic fever: While this is uncommon in developed countries, rheumatic fever can cause inflammation of the valves and therefore result in mitral regurgitation.
- Congenital

## Symptoms:

- Most patients with MR are asymptomatic, and patients suffering from mild to moderate MR may stay largely asymptomatic indefinitely. Symptoms tend to be due to failure of the left ventricle, arrhythmias or pulmonary hypertension. This may present as fatigue, shortness of breath and oedema.

## Signs:

- The murmur heard on auscultation of the chest is typically a pansystolic murmur described as "blowing". It is heard best at the apex and radiating into the axilla. S1 may be quiet as a result of incomplete closure of the valve. Severe MR may cause a widely split S2

## Investigations:

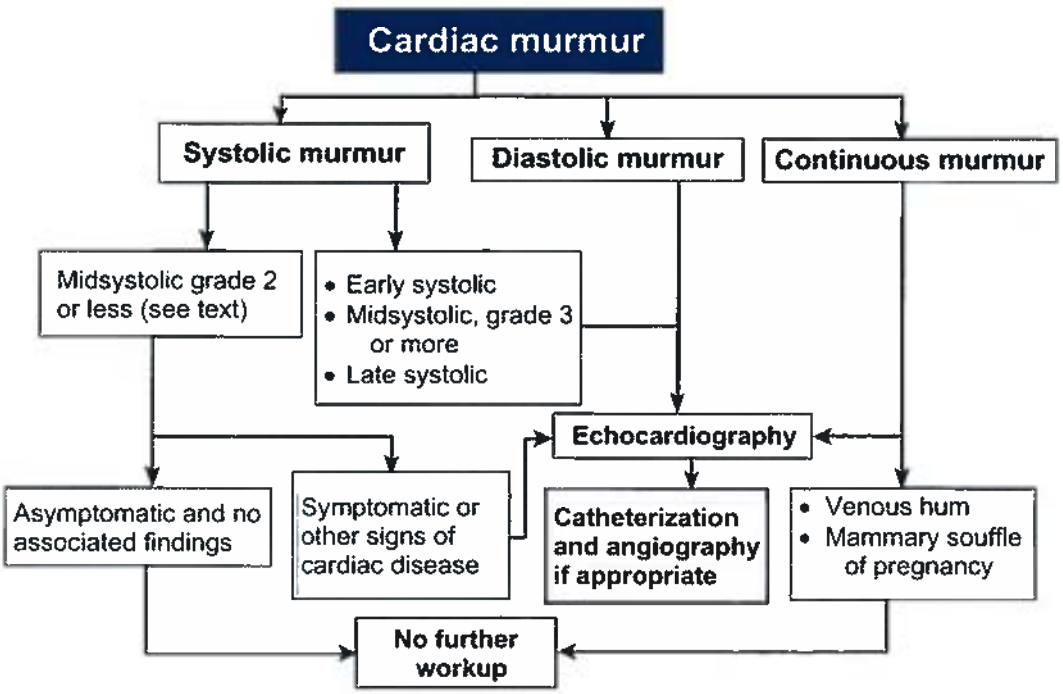
- ECG may show a broad P wave, indicative of atrial enlargement
- Cardiomegaly may be seen on chest x-ray, with an enlarged left atrium and ventricle
- Echocardiography is crucial to diagnosis and to assess severity

## Treatment options

- Medical management in acute cases involves nitrates, diuretics, positive inotropes and an intra-aortic balloon pump to increase cardiac output
- If patients are in heart failure, ACE inhibitors may be considered along with beta-blockers and spironolactone
- In acute, severe regurgitation, surgery is indicated
- The evidence for repair over replacement is strong in degenerative regurgitation, and is demonstrated through lower mortality and higher survival rates
- When this is not possible, valve replacement with either an artificial valve or a pig valve is considered

Most common cause of **MS** >>> **Rheumatic fever**
Most common cause of **MR** >>> **Myxomatous degeneration**

### Summary of valvular heart diseases



# Principal Causes of Heart Murmurs

## Systolic Murmurs

### Early Systolic

- **Mitral—acute MR**
- **VSD**
  - Muscular
  - Nonrestrictive with pulmonary hypertension
- **Tricuspid**—TR with normal pulmonary artery pressure

### Midsystolic

- **Aortic**
  - Obstructive
    - Supravalvular—supravalvular aortic stenosis, coarctation of the aorta
    - Valvular—aortic stenosis and sclerosis
    - Subvalvular—discrete, tunnel, or hypertrophic cardiomyopathy (HCM)
  - Increased flow, hyperkinetic states, AR, complete heart block
  - Dilation of ascending aorta, atheroma, aortitis
- **Pulmonary**
  - Obstructive
    - Supravalvular—pulmonary artery stenosis
    - Valvular—pulmonic valve stenosis
    - Subvalvular—infundibular stenosis (dynamic)
  - Increased flow, hyperkinetic states, left-to-right shunt (e.g., ASD)
  - Dilation of pulmonary artery

### Late Systolic

- Mitral—MVP, acute myocardial ischemia
- Tricuspid—tricuspid valve prolapsed

### Holosystolic

- Atrioventricular valve regurgitation (MR, TR)
- Left-to-right shunt at ventricular level (VSD)

## Diastolic Murmurs

### Early Diastolic

- **Aortic regurgitation**
  - Valvular—congenital (bicuspid valve), rheumatic deformity, endocarditis, prolapse, trauma, postvalvulotomy

- Dilation of valve annulus—aortic dissection, annuloaortic ectasia, cystic medial degeneration, hypertension, ankylosing spondylitis
- Widening of commissures—syphilis

- **Pulmonic regurgitation**
  - Valvular—postvalvulotomy, endocarditis, rheumatic fever, carcinoid
  - Dilation of valve annulus—pulmonary hypertension, Marfan syndrome
  - Congenital—isolated or associated with tetralogy of Fallot, VSD, pulmonic stenosis

**Middiastolic**

- **Mitral**
  - MS
  - Carey Coombs murmur (middiastolic apical murmur in acute rheumatic fever)
  - Increased flow across nonstenotic mitral valve (e.g., MR, VSD, PDA, high-output states, complete heart block)
- **Tricuspid**
  - Tricuspid stenosis
  - Increased flow across nonstenotic tricuspid valve (e.g., TR, ASD, anomalous pulmonary venous return)
- **Left and right atrial tumors (myxoma)**
- **Severe or eccentric AR (Austin Flint murmur)**

**Late Diastolic**

- Presystolic accentuation of MS murmur
- Austin Flint murmur of severe or eccentric AR

## Continuous Murmurs

- PDA
- AV fistula
- Ruptured sinus of Valsalva aneurysm
- Aortic septal defect
- Cervical venous hum
- Anomalous left coronary artery
- Proximal coronary artery stenosis
- Mammary souffle of pregnancy
- Pulmonary artery branch stenosis
- Bronchial collateral circulation
- Small (restrictive) ASD with MS
- Intercostal arteriovenous fistula

## Recommendations for Echocardiography in the Evaluation of Cardiac Murmurs

### Class I

- Echocardiography is recommended for asymptomatic patients with diastolic murmurs, continuous murmurs, holosystolic murmurs, late systolic murmurs, murmurs associated with ejection clicks, or murmurs that radiate to the neck or back.
- Echocardiography is recommended for patients with heart murmurs and symptoms or signs of heart failure, myocardial ischemia/infarction, syncope, thromboembolism, infective endocarditis, or other clinical evidence of structural heart disease.
- Echocardiography is recommended for asymptomatic patients who have grade 3 or louder mid- peaking systolic murmurs.

### Class IIa

- Echocardiography can be useful for the evaluation of asymptomatic patients with murmurs associ- ated with other abnormal cardiac physical findings or murmurs associated with an abnormal ECG or chest x-ray.
- Echocardiography can be useful for patients whose symptoms and/or signs are likely noncardiac in origin but in whom a cardiac basis cannot be excluded by standard evaluation.

### Class III

- Echocardiography is not recommended for patients who have a grade 2 or softer midsystolic murmur identified as innocent or functional by an experienced observer.

## Mitral valve prolapse (MVP)

Mitral valve prolapse is **common**, occurring in **around 5-10 % of the population** and it is more common in **females.**

It is usually idiopathic but may be associated with a wide variety of cardiovascular disease and other conditions

### Associations:

- congenital heart disease: PDA, ASD
- cardiomyopathy
- **Turner's** syndrome
- **Marfan's** syndrome, Fragile X
- **Osteogenesis imperfecta**
- **Pseudoxanthoma elasticum**
- **Wolff-Parkinson White syndrome**
- **Long-QT syndrome**
- **Ehlers-Danlos Syndrome**
- **Polycystic kidney disease**

### Features:

- Patients may complain of atypical chest pain or palpitations
- Mid-systolic click (occurs later if patient squatting)
- Late systolic murmur (longer if patient standing)
- Complications: mitral regurgitation, arrhythmias (including long QT), emboli, sudden death

### Treatment:

- Mild to moderate >>> **Bisoprolol** and **follow** up echo every 2-3 years.
- Severe with LV dysfunction >>> **MVR**.
- Endocarditis prophylaxis is not required according to NICE guidelines.

**NB: In acromegaly (it is NOT a common association).**

## Tricuspid regurgitation

### Signs:

- **Pan-systolic murmur**
- **Giant V waves in JVP**
- **Pulsatile hepatomegaly**
- **Left parasternal heave**

## Causes:

- Right ventricular dilation
- **Pulmonary hypertension e.g. COPD**
- Rheumatic heart disease
- **Infective endocarditis (especially intravenous drug users)**
- **Ebstein's anomaly**
- Carcinoid syndrome

# Prosthetic heart valves

The most common valves which need replacing are the aortic and mitral valve. There are 2 main options for replacement: biological (bio prosthetic) or mechanical.

| Biological (bio prosthetic) (tissue) valves | Mechanical valves |
|---|---|
| ➢ Usually bovine or **porcine** in origin.<br>➢ Major disadvantage is **structural deterioration and calcification with stenosis over time.**<br>➢ So typically, must be **replaced** within 5 to **10** years.<br>➢ **Older** patients (> 65 years for aortic valves and > 70 years for mitral valves) receive a bio prosthetic valve.<br>➢ **Young female** when her desire to have children and not to take anticoagulant medication.<br>➢ Long-term anticoagulation not usually needed. Warfarin may be given for the first 3 months depending on patient factors. **Low-dose aspirin is given long-term.** | ➢ **The most common type now** implanted is the **bileaflet** valve. (Ball-and-cage valves are rarely used nowadays).<br>➢ Mechanical valves have **a low failure rate.**<br>➢ Major disadvantage is the increased risk of thrombosis **meaning long-term anticoagulation** is needed. **Aspirin is normally given in addition** unless there is a contraindication.<br>➢ Target INR:<br>o Aortic: 2.0-3.0<br>o Mitral: 2.5-3.5 |

**Prosthetic heart valves >> antithrombotic therapy:**

- Bioprosthetic >> Aspirin
- Mechanical >> warfarin + aspirin

Prosthetic heart valves >>> mechanical valves last longer and tend to be given to younger patients

**NB**: Following the 2008 NICE guidelines for prophylaxis of endocarditis antibiotics are no longer recommended for common procedures such as dental work.

**NB:** If patient has prosthetic valve thrombosis (PVT) resulting in shock. This complication occurs in 0.03 to 5.5%annually with equal frequency in bioprosthesis and mechanical valves. It is more common in mitral prosthesis and with subtherapeutic anticoagulation.The best diagnostic modality is transoesophageal echocardiography; however transthoracic echocardiography is the initial choice in sick patients, and then if the diagnosis is not confirmed, a TEE can be done. Thorombolytic therapy should be given for patients in pulmonary oedema or hypotension. In stable patients, surgery is a better option for left-sided PVT, while right-sided PVT should be treated with thrombolytic agents. Serial echocardiography should be performed, and if the response is inadequate repeat thrombolytic therapy can be given.

**PVT (prosthetic valve thrombosis)** with **shock**, hypotension or **pulmonary oedema** >>> Nest step is **Thrombolytic therapy**

**Young female** patient with bicuspid aortic valve and wishes to **start family** >>> **Biological (bio prosthetic) (porcine) valve replacement**

# Infective endocarditis

## Infective endocarditis

The **strongest risk factor** for developing infective endocarditis **is a previous episode of endocarditis.**

**The following types of patients are affected:**

- Previously normal valves (50%, typically acute presentation)
- Rheumatic valve disease (30%)
- Prosthetic valves
- Congenital heart defects
- Intravenous drug users (IVDUs, e.g. Typically causing tricuspid lesion)

### Causes:

- **Streptococcus viridans:** Streptococcus mitis following dental work, (most common cause - 40-50%)
- Staphylococcus aureus (coagulase **positive** +ve) (especially acute presentation, **IVDUs).**
- Staphylococcus epidermidis (coagulase **negative** –ve) (especially **prosthetic** valves).
- Streptococcus Bovis is associated with colorectal cancer.
- **Non-bacterial thrombotic endocarditis**: SLE (Liebman-Sacks), malignancy (**marantic endocarditis).**

### Culture negative causes:

- Prior antibiotic therapy
- Brucella
- Bartonella
- Coxiella burnetii
- HACEK: Haemophilus, Actinobacillus, Cardiobacterium, Eikenella, Kingella)

**Most common cause of endocarditis:**

- **Streptococcus viridans**.
- Staphylococcus epidermidis if < 2 months post valve surgery.

**NB:** Following prosthetic valve surgery **Staphylococcus epidermidis** is the most common organism in **the first 2 months** and is usually the result of perioperative contamination.

After 2 months the spectrum of organisms which cause endocarditis return to normal, except with a slight increase in Staph aureus infections.

**NB:** EX. Pt. with sigmoid adenocarcinoma + fever + SOB >>> Echo >>> IEC (*Streptococcus bovis*).

**NB: Coxiella** infection is widespread in **domestic and farm animals**, it usually spreads between animals by ticks which acts as reservoirs of infection.

Infection may be spread via unpasteurised milk.

Coxiella is usually diagnosed via **complement fixation**.

**Treatment: Doxycycline**

A dangerous complication of **Aortic valve endocarditis** that it can cause **aortic root abscess** which can cause damage/ erosion to the **AV node** resulting in **prolongation of the PR interval** on 12 lead ECG.

So **ECGs** should be performed **daily** to monitor for infections involving the aortic root/aortic valve.

## Infective endocarditis: Modified Duke Criteria

### Infective endocarditis diagnosed if:

- Pathological criteria positive, or
- 2 major criteria, or
- 1 major and 3 minor criteria, or
- 5 minor criteria

### Pathological criteria:

**Positive histology** or **positive microbiology** of **pathological material** obtained at autopsy or cardiac surgery (valve tissue, vegetations, embolic fragments or intracardiac abscess content)

## Major criteria:

### 1) Positive blood cultures:

- It should be at least **3 sets blood culture samples from 3 different sites**: they are **positive** in **75%** of cases of **bacterial** endocarditis.
- Because bacteraemia may be periodic, blood cultures should not be taken simultaneously, but should be taken **sequentially from 3 different sites, 1 hour apart.**
- **Draw 3 samples of blood from 3 different sites with the first separated from the last by at least one hour over 24 hours.**
- **Two positive** blood cultures showing typical organisms consistent with infective endocarditis, such as *Streptococcus viridans* and the HACEK group, or
- **Persistent bacteraemia from two blood cultures taken > 12 hours apart or three** or more positive blood cultures where the pathogen is less specific such as *Staph aureus* and *Staph epidermidis*, or
- **Positive serology** for *Coxiella burnetii*, *Bartonella* species or *Chlamydia psittaci*, or
- **Positive molecular assays for specific gene targets**

### 2) Evidence of endocardial involvement:

- Positive **echocardiogram:** oscillating structures, abscess formation, new valvular regurgitation or dehiscence of prosthetic valves.

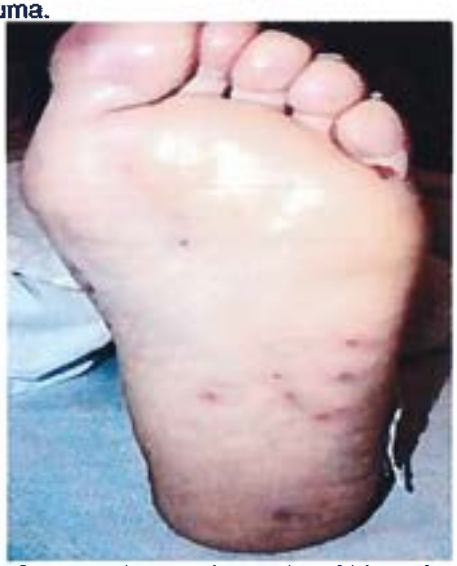
It is also important to remember that a normal echocardiogram **does not** exclude infective endocarditis.

## Minor criteria:

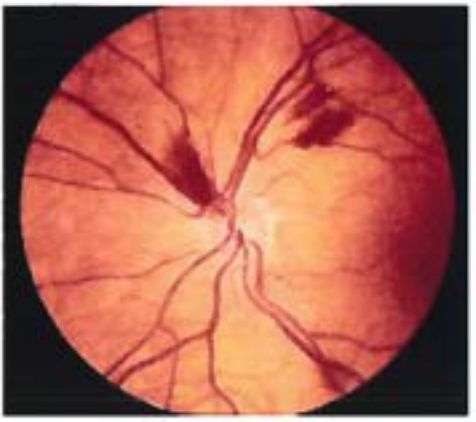
- **Predisposing** heart condition or **intravenous drug use.**
- Microbiological evidence does not meet major criteria.
- **Fever > 38°C.**
- **Vascular phenomena:** major emboli, splenomegaly, clubbing, splinter haemorrhages, petechiae or purpura.
- **Immunological** phenomena: glomerulonephritis, Osler's nodes, Roth spots, Janeway lesions.

Splinter hemorrhages appearing as red linear streaks under the nail plate and within the nail bed. Although endocarditis can cause this, splinter hemorrhages are more commonly seen in psoriasis and trauma.

Janeway lesions on the palm of a woman hospitalized with acute bacterial endocarditis. These were not painful.



Osler node causing pain within pulp of the big toe in the same woman hospitalized with acute bacterial endocarditis. (Osler nodes are painful—remember "O" for Ouch and Osler.) Note the multiple painless flat Janeway lesions over the sole of the foot.



Roth spots that are retinal hemorrhages with white centers seen in bacterial endocarditis. These can also be seen in leukemia and diabetes.

# Infective endocarditis: prognosis and management

## Poor prognostic factors:

- **Staph aureus** infection **acute** endocarditis (see below).
- **I.V** drug abuse (often left and right sided disease).
- Infection of the **aortic** rather than mitral valve.
- **Prosthetic** valve endocarditis (esp 'early', acquired during surgery).
- **Culture negative** endocarditis.
- **Low complement** levels.
- **Old age.**
- **IDDM**.
- Severe co-morbidities

## Other factors that are crucial in prognostic assessment are:

- Endocarditis due to **fungus** or Gram **negative bacilli.**
- Endocarditis **complications** including heart failure, renal failure, stroke, septic shock and periannular complications, and
- **Echocardiographic** findings including severe left sided valve regurgitation, low LV EF%, pulmonary hypertension, large vegetations and severe prosthetic valve dysfunction.

**NB:** Infective endocarditis >>> streptococcal infection (Subacute bacterial endocarditis (Streptococcus viridans) >>> carries a good prognosis.

## Mortality according to organism:

- staphylococci - 30%
- bowel organisms - 15%
- streptococci - 5%

**Current antibiotic guidelines** (source: British National Formulary)

| Scenario | Suggested antibiotic therapy |
|---|---|
| **Initial blind therapy** | **Native valve:**<br>• **Amoxicillin**, consider adding low-dose **gentamicin**<br>**If penicillin allergic, MRSA or severe sepsis:**<br>• **vancomycin** + low-dose **gentamicin**<br>**If prosthetic valve:**<br>• **Vancomycin + rifampicin + low-dose gentamicin.** |
| Native valve endocarditis caused by staphylococci | **Flucloxacillin + gentamicin**<br>**If penicillin allergic or MRSA:**<br>Vancomycin + gentamicin. |
| Prosthetic valve endocarditis caused by staphylococci | **Flucloxacillin + Rifampicin + low-dose gentamicin**<br>**If penicillin allergic or MRSA:**<br>• Vancomycin + Rifampicin + low-dose gentamicin. |
| **Endocarditis caused by fully-sensitive streptococci (e.g. viridans)** | **Benzylpenicillin.**<br>**If penicillin allergic:**<br>• Vancomycin + low-dose gentamicin |
| Endocarditis caused by less sensitive streptococci | **Benzylpenicillin + low-dose gentamicin**<br>**If penicillin allergic:**<br>• Vancomycin + low-dose gentamicin |

The most useful laboratory test for monitoring the response to IEC treatment (which is usually obvious clinically) is **serial CRP estimation**. This is of much more use than the ESR, which is much slower to fall.

IEC caused by **candida albicans** over a **bicuspid aortic valve** in **IV drug abuser** patient >>> **Aortic valve replacement followed by Amphotericin B IV for 6 wks.**
**In Intravenous drug abuser (IVDA)** a **MRSA** is the causative organism in about **60-70%** of cases with **haematogenous spread** of bacteria resulting in **frontal lobe abscess** >>> **IV flucloxacillin + gentamicin** is the combination of choice till the result of culture.
If MRSA is confirmed >>> **IV vancomycin + gentamicin.**

**Teicoplanin** has a similar spectrum of antimicrobial activity to vancomycin, but has slightly more anti-streptococcal activity than vancomycin and slightly less anti-staphylococcal activity. It is **not** a first line agent in the ttt of endocarditis.

**EX:** A young male patient after **RTA** and ORIF of # at left tibia and fibula, then after 1 wk. develops fever (38.5°C), tachycardia (130 bpm), low BP (100/60 mmHg), splinter haemorrhage on finger nails, systolic murmur, rise serum creatinine, urine: blood+, protein +, leucocytes+ >>> **? IEC** due to **staph** due to his **extensive trauma** >>> **initial** blind ttt before results of blood culture is >>> **IV flucloxacillin + IV gentamicin.**

## Indications for surgery:

- **Severe valvular incompetence.**
- Severe mitral regurgitation causing refractory pulmonary oedema.
- Severe mitral regurgitation with signs of pulmonary hypertension.
- **Cardiac failure,** as a result of **valve destruction,** refractory to standard medical treatment.
- **Aortic abscess** (often indicated by a **lengthening PR interval).**
- Infections **resistant** to antibiotics such as **fungal** infections or **multi resistant** organisms, brucella, coxiella, pseudomonas aeruginosa, vancomycin-resistant enterocoli.
- **Persistent** bacteraemia despite appropriate antibiotic therapy.
- **Extension** of infection to an extravalvular site.
- **Recurrent emboli** after antibiotic therapy
- **Early prosthetic** valve endocarditis (within 2 months).
- **Dehiscence or obstruction of a prosthetic valve.**
- **Persistent fever for 10 days in culture-negative prosthetic valve endocarditis.**

Valve surgery may be deferred until the patient is apyrexial unless there is haemodynamic compromise, larger vegetations are seen or an abscess present.

**The ESC European Society of Cardiology makes the following recommendations with regard to infective endocarditis related to cardiac devices:**

- **Prolonged antibiotic therapy** and **device removal** are recommended.
- Percutaneous extraction is recommended in most patients with cardiac devices even those with large (>10 mm) vegetations.
- After device extraction, **reassessment** of the need for re-implantation is recommended, and
- Routine **antibiotic** prophylaxis is recommended before device implantation.

# Infective endocarditis: prophylaxis

The NICE guidelines have fundamentally changed the approach to infective endocarditis prophylaxis. What is not yet clear is if there are any circumstances in which NICE would recommend using antibiotic prophylaxis.

The guidelines from NICE have radically changed the list of procedures for which antibiotic prophylaxis is recommended.

**NICE recommends the following procedures do not require prophylaxis:**

- Dental procedures.
- Upper and lower gastrointestinal tract procedures
- Genitourinary tract; this includes urological, gynaecological and obstetric procedures and childbirth.
- Upper and lower respiratory tract; this includes ear, nose and throat procedures and bronchoscopy.

**The guidelines do however suggest:**

- Any episodes of infection in people at risk of infective endocarditis should be investigated and treated promptly to reduce the risk of endocarditis developing.
- If a person at risk of infective endocarditis is receiving antimicrobial therapy because they are undergoing a gastrointestinal or genitourinary **procedure at a site where there is a suspected infection they should be given an antibiotic that covers organisms that cause infective endocarditis**

According to NICE guidelines, antibiotic **Prophylaxis against infective endocarditis (CG64)** is **not recommended in common cardiac valve abnormalities.**

**Prophylaxis is only recommended in those patients who are at highest risk of adverse outcomes on the development of endocarditis.** These

## patient groups include:

- **Previous endocarditis.**
- **Acquired valvular heart disease with stenosis or regurgitation.**
- **HOCM.**
- **Prosthetic** cardiac valve or prosthetic material used for cardiac valve repair.
- **Unrepaired congenital cyanotic heart disease** including palliative shunts and conduits.

- **Completely repaired congenital heart defect** with **prosthetic** material or device, whether placed by surgery or by catheter intervention, during the first 6 months after the procedure.
- **Repaired congenital** heart disease with **residual defects** (persisting leaks or abnormal flow) at the site or adjacent to the site of a prosthetic patch or prosthetic device (which inhibit endothelialisation).
- **Cardiac transplantation recipients** who develop cardiac **valve** abnormalities.

Erythema marginatum is seen in around 10% of children with rheumatic fever. It is rare in adults

# Pericardial diseases

## Pericarditis

Pericarditis is one of the differentials of any patient presenting with chest pain.

**Pericarditis = Triad of**

1) Chest pain worse on lying down,
2) Pericardial friction rub and
3) Classical ECG changes.

### Features:

- Chest pain: may be **pleuritic.** It is **often worse by lying down, relieved by sitting forwards.**
- Other symptoms: non-productive cough, dyspnoea & **flu**-like symptoms.
- **Pericardial rub.**
- **Tachycardia.**
- **Tachypnoea.**
- A modest rise in troponin is in around **one-third** of acute pericarditis.
- Raised **TLC, ESR** and **CPK** are to be expected.

### Causes:

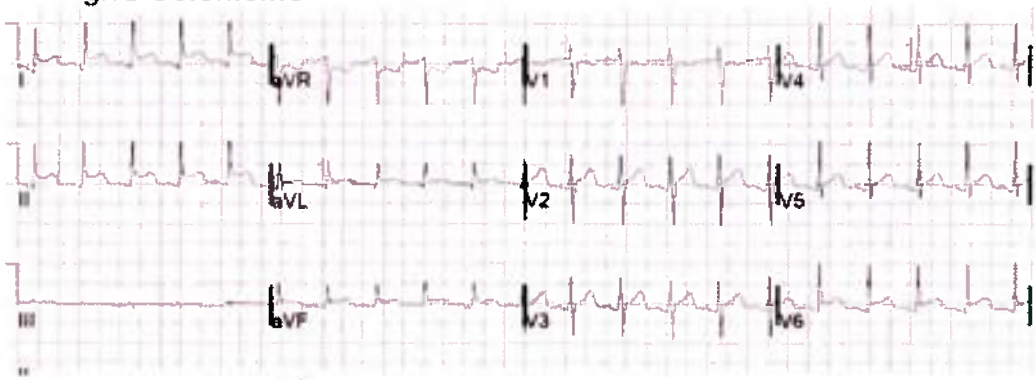
- Viral infections: **Coxsackie B virus,** adenovirus, echovirus and influenza.
- TB
- **Uraemia**: causes **'fibrinous' pericarditis.**
- Trauma
- **Post-myocardial infarction, Dressler's syndrome.**
- Auto immune connective tissue disease: **RA**
- Malignancy
- Radiotherapy
- Hypothyroidism
- Drugs: Hydralazine

### Investigations

- **ECG changes**
  - the changes in pericarditis are often **global/widespread**, as opposed to the 'territories' seen in ischaemic events
  - 'saddle-shaped' ST elevation
  - **PR depression: most specific ECG marker for pericarditis**
- all patients with suspected acute pericarditis should have transthoracic echocardiography

## Treatment: (If symptomatic)

- **NSAIDs** (e.g. **Brufen** 800 mg 1x4)
- **Colchicine** is useful both in **acute** episode and to **prevent recurrence.**
- **Prednisolone** (if pain fails to settle within 48 hrs), it is considered to in patients who fail to respond to NSAIDs and colchicine.
- **Pericardiectomy**: is only indicated once thorough medical therapy has failed.
- Patients should be told to **reduce physical activity** for a number of days after diagnosis.
- Recurrent pericarditis with not well respond to NSAID so, you have to give **Colchicine**




ECG showing pericarditis. Note the widespread nature of the ST elevation and the PR depression

**NB**: In patient with **uraemic pericarditis Haemodialysis (heparin-free)** is **urgently** required to correct the uraemia which in turn will improve the symptoms of pericarditis.

# Constrictive pericarditis

## Causes

- any cause of pericarditis
- particularly TB

## Features

- dyspnoea
- right heart failure: elevated JVP, ascites, oedema, hepatomegaly
- JVP shows prominent x and y descent
- pericardial knock - loud S3
- Kussmaul's sign is positive

## CXR

- pericardial calcification

The key differences between constrictive pericarditis and cardiac tamponade are summarized in the table below:

| | Cardiac tamponade | Constrictive pericarditis |
|---|---|---|
| JVP | Absent Y descent | X + Y present |
| Pulsus paradoxus | Present | Absent |
| Kussmaul's sign* | Rare | Present |
| Characteristic features | | Pericardial calcification on CXR |

A commonly used mnemonic to remember the absent Y descent in cardiac tamponade is TAMponade = TAMpaX

*a paradoxical rise in JVP during inspiration

# Cardiac tamponade

## Features:

- Dyspnoea
- **Raised JVP**, with an **absent Y descent** - this is due to the limited right ventricular filling
- **Tachycardia**
- **Hypotension**
- **Muffled heart sounds**
- **Pulsus paradoxus**
- ECG: **low voltage**, **electrical alternans** (QRS complexes with alternating amplitude).

The key differences between cardiac tamponade and constrictive pericarditis are summarised in the table below:

| | Cardiac tamponade | Constrictive pericarditis |
|---|---|---|
| JVP | Absent Y descent | **X + Y present** |
| Pulsus paradoxus | **Present** | Absent |
| Kussmaul's sign | Rare | **Present** |
| Characteristic features | | Pericardial calcification on CXR (dt: TB, irradiation) |

A commonly used mnemonic to remember the absent Y descent in cardiac tamponade is **TAMponade = TAMpaX**

**Pulsus paradoxus** (a greater than 10 mmHg fall in systolic BP on inspiration) i.e. **faint or absent pulsation during deep inspiration** but this is more commonly seen in cardiac tamponade than constrictive pericarditis.

**Kussmaul's sign** (a **rise in the JVP on inspiration**) is more likely to be seen in constrictive pericarditis than cardiac tamponade.

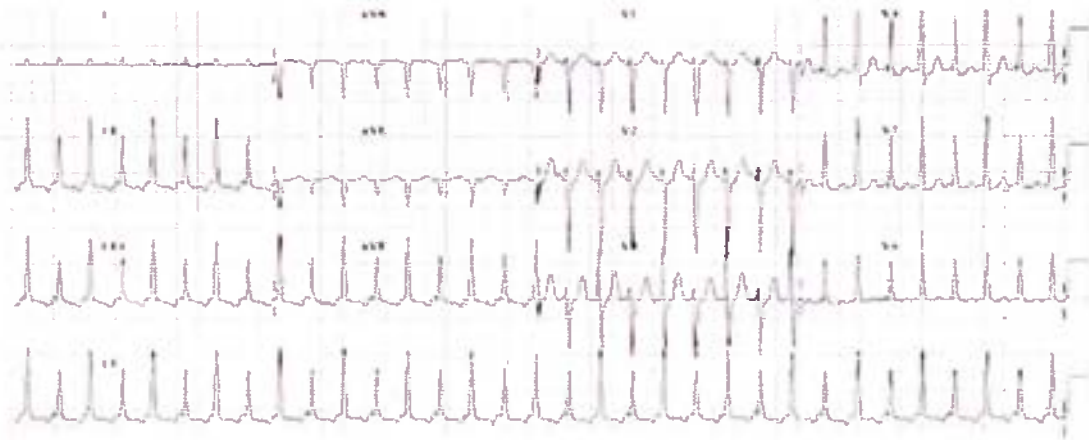
Pt with dyspnoea+ distant heart sound + CXR shows a **thin rim of calcification** surrounding the cardiac outline >> **constrictive pericarditis** >> the most probable cause for this is prior **TB** infection (**tuberculous pericarditis**), **irradiation** and any cause of purulent pericarditis.

The most common cause of **constrictive pericarditis** worldwide is **tuberculous pericarditis.**

**Causes** of pericardial effusion: Neoplasia (as **mesothelioma** dt asbestos exposure), **Infection (TB, HIV)**, Valvular disease (as in **IEC**), Trauma, Uraemia, Myxoma

## Management

- urgent pericardiocentesis



An ECG demonstrating electrical alternans. Note the alternation of QRS complex amplitude between beats.

# Myocarditis

Myocarditis describes inflammation of the myocardium. There are a wide range of underlying causes. It should be particularly considered in younger patients who present with chest pain.

## Causes:

- a virus, such as **the flu or Covid-19** (British Heart Foundation)
- **Viral: Coxsackie, HIV**
- **Bacteria: diphtheria**, clostridia
- **Spirochaetes: Lyme** disease
- **Protozoa: Chagas'** disease, **Toxoplasmosis.** (NO Leishmaniasis)
- **Autoimmune**
- **Drugs: doxorubicin**

**NB: Syphilis** involves the cardiovascular system, commonly in the form of **ascending aortic aneurysm** and **aortic regurgitation** (NOT Myocarditis).

## Presentation

- usually young patient with an acute history
- chest pain
- dyspnoea
- arrhythmias

## Investigations

- bloods
  - ↑ inflammatory markers in 99%
  - ↑ cardiac enzymes
  - ↑ BNP
- ECG
  - tachycardia
  - arrhythmias
  - ST/T wave changes including ST-segment elevation and T wave inversion

## Management

- treatment of underlying cause e.g. antibiotics if bacterial cause
- supportive treatment e.g. of heart failure or arrhythmias

## Complications

- heart failure
- arrhythmia, possibly leading to sudden death
- dilated cardiomyopathy: usually a late complication

# Ischemic heart disease

## Chest pain: Assessment of patients with suspected cardiac chest pain

the clinical presentation of acute coronary syndromes (ACS) is broad.
It ranges from cardiac arrest, electrical or hemodynamic instability with cardiogenic shock (CS) due to ongoing ischaemia or mechanical complications such as severe mitral regurgitation, to patients who are already pain free again at the time of presentation.
The leading symptom initiating the diagnostic and therapeutic cascade in patients with suspected ACS is acute chest discomfort described as pain, pressure, tightness, and burning.
Chest pain-equivalent symptoms may include dyspnea, epigastric pain, and pain in the left arm. Based on the electrocardiogram (ECG), two groups of patients should be differentiated

NICE issued guidelines on the 'Assessment and diagnosis of recent onset chest pain or discomfort of suspected cardiac origin'.

**Patients presenting with acute chest pain:**
Immediate management of suspected acute coronary syndrome (ACS):
**Please refer to NICE guidelines 2020**

- Glyceryl trinitrate.
- **Aspirin 300mg**. NICE do not recommend giving other antiplatelet agents (i.e., Clopidogrel) outside of hospital.
- **Offer fondaparinux to people with unstable angina or NSTEMI who do not have a high bleeding risk, unless they are undergoing immediate coronary angiography. [2020]**
- Do not routinely give oxygen, only give if sat. < 94%*
- Perform an ECG as soon as possible but do not delay transfer to hospital.
- **A normal ECG does not exclude ACS**.

**Referral:**

- Current chest pain or chest pain in the last 12 hours with an abnormal ECG: emergency admission.
- Chest pain 12-72 hours ago: refer to hospital the same-day for assessment.
- Chest pain > 72 hours ago: perform full assessment with ECG and troponin measurement before deciding upon further action

**NICE suggest the following in terms of oxygen therapy:**

- **Do not routinely administer oxygen**, but monitor oxygen saturation using pulse oximetry as soon as possible, ideally before hospital admission. Only offer supplemental oxygen to:
- People with oxygen saturation (SpO2) of less than 94% who are not at risk of hypercapnic respiratory failure, aiming for SpO2 of 94-98%
- People with COPD who are at risk of hypercapnic respiratory failure, to achieve a target SpO2 of 88-92% until blood gas analysis is available.

**Patients presenting with stable chest pain:**

NICE guidelines for assessment of patients with stable chest pain suggest an approach where the risk of a patient having coronary artery disease (CAD) is calculated based on their symptoms (whether they have typical angina, atypical angina or non-anginal chest pain), age, gender and risk factors.

**NICE define anginal pain as the following:**

- **constricting discomfort** in the front of the chest, neck, shoulders, jaw or arms
- **precipitated by** physical exertion
- **relieved by** rest or GTN in about 5 minutes
  - patients with all 3 features have typical angina
  - patients with 2 of the above features have atypical angina
  - patients with 1 or none of the above features have non-anginal chest pain

**If patients have typical anginal symptoms and a risk of CAD is greater than 90%** then **coronary angiography must be performed..**

It should be noted **that all men over the age of 70 years who have typical anginal symptoms fall into this category.**

For patients with an estimated risk of 10-90% the following investigations are recommended. **Note the absence of the exercise tolerance test:**

| Estimated likelihood of CAD | Diagnostic testing |
|---|---|
| **61-90%** | **Coronary angiography** |
| **30-60%** | **Functional imaging**, for example:<br>• **Myocardial perfusion scan with SPECT.**<br>• **Dobutamine Stress echocardiography.**<br>• First-pass contrast-enhanced magnetic resonance (MR) perfusion<br>• MR imaging for stress-induced wall motion abnormalities. |
| **10-29%** | **CT calcium scoring** |

If patient has symptoms suggestive of IHD with normal ECG, the diagnosis should be confirmed with non-invasive functional scanning such as myocardial perfusion scan with SPECT.

According to NICE guidance, where the diagnosis of CAD is suspected but not confirmed, **exercise testing is no longer recommended.**

**NB: Exercise ECG is not useful in patients with:**

- Conduction abnormalities: e.g., RBBB.
- Resting ECG abnormalities like ST segment depression of > 1 mm.
- WPWS
- Those with ventricular pacing rhythm.
- Those on digoxin.

**Pharmacological stress in form of dobutamine stress echocardiography** can be used in patients who are **unable** to exercise because of stroke, PVD or arthritis, although it also should be **avoided** in conduction abnormalities, resting ECG ischaemic abnormalities, **ectatic vessles** and WPWS.

When comparing the dobutamine stress versus thallium scanning, **thallium has greater sensitivity**, versus **greater specificity for dobutamine** with respect to CAD.
So, in a case of **intermediate** likelihood CAD, **thallium** is the preferred option.

## Angina pectoris: drug management

The management of stable angina comprises lifestyle changes, medication, percutaneous coronary intervention and surgery.

### Medications:

**Offer** people with acute STEMI a single loading dose of 300-mg aspirin as soon as possible unless there is clear evidence that they are allergic to it.
Do not offer routine glycoprotein IIb/IIIa inhibitors or fibrinolytic drugs before arrival at the catheter laboratory to people with acute STEMI for whom primary PCI is planned.

- All patients should receive **statin** in the absence of any contraindication.
- **Sublingual glyceryl trinitrate** to abort angina attacks.
- **NICE recommend** using **either a beta-blocker** or a **calcium channel blocker** first-line based on 'comorbidities, contraindications and the person's preference'.
- **If a calcium channel blocker is used as monotherapy** a rate-limiting one such as verapamil or diltiazem should be used.

- **If a CCB is used in combination with a beta-blocker** then use a long-acting dihydropyridine calcium-channel blocker (e.g. modified-release nifedipine).
- Remember that beta-blockers should not be prescribed concurrently with verapamil (risk of complete heart block) and diltiazem should be used with caution due to the risk of bradycardia.
- Verapamil and diltiazem should be avoided with BB and with those who has CHF.
- If there is a poor response to initial treatment then medication should be increased to the maximum tolerated dose (e.g. **for atenolol 100 mg OD,** however, **Fatigue** is a frequent side effect of atenolol which typically is felt **2 hours** and beyond **after** taking the drug.).
- If a patient is still symptomatic **after monotherapy with a beta-blocker add a calcium channel blocker and vice versa.**
- If a patient is on monotherapy and cannot tolerate the addition of a calcium channel blocker or a beta-blocker then consider one of the following drugs: a **long-acting nitrate**, **ivabradine**, **nicorandil** or **ranolazine.**
- **Nicorandil** is a **Potassium-channel activator.**
- If a patient is taking both a beta-blocker and a calcium-channel blocker then only add a third drug whilst a patient is awaiting assessment for PCI or CABG.

## Acute coronary syndrome

Acute coronary syndrome (ACS) is an umbrella term covering a number of acute presentations of ischaemic heart disease.

### It covers a number of presentations, including

- ST elevation myocardial infarction (STEMI)
- non-ST elevation myocardial infarction (NSTEMI)
- unstable angina
  - considered to be present in patients with ischaemic symptoms suggestive of an ACS and no elevation in troponins, with or without electrocardiogram changes indicative of ischaemia
  - however, as a rise in troponins may take some hours it may be indistinguishable for NSTEMI initially and is therefore treated the same until the troponin result is known

Before we go into more detail into these presentations it's useful to take a step back and consider how such conditions develop.

ACS generally develops in patients who have ischaemic heart disease, either known or previously undetected. Ischaemic heart disease is a term synonymous with coronary heart disease and coronary artery disease. It describes the gradually build up of fatty plaques within the walls of the coronary arteries.

**This leads to two main problems:**

1) Gradual narrowing, resulting in less blood and therefore oxygen reaching the myocardium at times of increased demand. This results in angina, i.e. chest pain due to insufficient oxygen reaching the myocardium during exertion
2) The risk of sudden plaque rupture. The fatty plaques which have built up in the endothelium may rupture leading to sudden occlusion of the artery. This can result in no blood/oxygen reaching the area of myocardium.

Remember that there are a large number of factors which can increase the chance of a patient developing ischaemic heart disease:

| Unmodifiable risk factors | Modifiable risk factors |
|---|---|
| | Smoking |
| Increasing age | Diabetes mellitus |
| Male gender | Hypertension |
| Family history | Hypercholesterolaemia |
| | Obesity |

## Pathophysiology

**Ischaemic heart disease is a complex process which develops over a number of years. A number of changes can be seen:**

- initial endothelial dysfunction is triggered by a number of factors such as smoking, hypertension and hyperglycaemia
- this results in a number of changes to the endothelium including pro-inflammatory, pro-oxidant, proliferative and reduced nitric oxide bioavailability
- fatty infiltration of the subendothelial space by low-density lipoprotein (LDL) particles
- monocytes migrate from the blood and differentiate into macrophages. These macrophages then phagocytose oxidized LDL, slowly turning into large 'foam cells'. As these macrophages die the result can further propagate the inflammatory process.
- smooth muscle proliferation and migration from the tunica media into the intima results in formation of a fibrous capsule covering the fatty plaque.

## Complications of atherosclerosis

**Once a plaque has formed a number of complications can develop:**

- the plaque forms a physical blockage in the lumen of the coronary artery. This may cause reduced blood flow and hence oxygen to the myocardium, particularly at times of increased demand, resulting clinically in angina
- the plaque may rupture, potentially causing a complete occlusion of the coronary artery. This may result in a myocardial infarction

## Symptoms and signs

**The classic and most common feature of ACS is chest pain.**

- typically central/left-sided
- may radiate to the jaw or the left arm
- often described as 'heavy' or constricting, 'like an elephant on my chest'
- it should be noted however in real clinical practice patients present with a wide variety of types of chest pain and patients/doctors may confuse ischaemic pain for other causes such as dyspepsia
- certain patients e.g. diabetics/elderly may not experience any chest pain

**Other symptoms in ACS include:**

- dyspnoea
- sweating
- nausea and vomiting

**Patients presenting with ACS often have very few physical signs to elicit:**

- pulse, blood pressure, temperature and oxygen saturations are often normal or only mildly altered e.g. tachycardia
- if complications of the ACS have developed e.g. cardiac failure then clearly there may a number of findings
- the patient may appear pale and clammy

## Investigations

**The two most important investigations when assessing a patient with chest pain are:**

- ECG
- cardiac markers e.g. troponin

The table below shows a simplified correlation between ECG changes and coronary territories:

| | ECG changes | Coronary artery |
|---|---|---|
| Anterior | V1-V4 | Left anterior descending |
| Inferior | II, III, aVF | Right coronary |
| Lateral | I, V5-6 | Left circumflex |

Diagram showing the correlation between ECG changes and coronary territories in acute coronary syndrome

## Secondary prevention

**Patients who've had an ACS require lifelong drug therapy to help reduce the risk of a further event. Standard therapy comprises the following as a minimum:**

- aspirin
- a second antiplatelet if appropriate (e.g. clopidogrel)
- a beta-blocker
- an ACE inhibitor
- a statins.

The table below summaries the mechanism of action of drugs commonly used in the management of acute coronary syndrome:

| Medication | Mechanism of action |
|---|---|
| **Aspirin** | Antiplatelet - inhibits the production of **thromboxane A2** |
| **Clopidogrel** | Antiplatelet - inhibits **ADP** binding to its platelet receptor |
| **Enoxaparin** | **Activates antithrombin III**, which in turn potentiates the inhibition of coagulation factors **Xa** |
| **Fondaparinux** | **Activates antithrombin III**, which in turn potentiates the inhibition of coagulation factors **Xa** |
| **Bivalirudin** | **reversible direct thrombin inhibitor used as an anticoagulant in the management of acute coronary syndrome.** |

NICE guidelines of NSTEMI/UA are based **on 6 month mortality risk**:

- **If > 1.5%** >>> **Clopidogrel for 12 months.**
- **If > 3%** >>>> IV GP IIb/IIIa receptor antagonists + Coronary angiography within 96 hours.

**EX**: Patient at CCU post-acute **MI** with **PCI** and **stent** and he is on ASA + Plavix + Clexane, now he has melena, drop of BP with postural hypotension and low Hb >>> after giving IV fluids and packed RBCs transfusion **NEXT STEP WILL BE Stop anticoagulant, but keep both ASA and Plavix.**

**M**anagement of anti-platelet agents and anti-coagulation is a source of considerable debate when haemorrhage is seen post PCI.

In this case a significant upper GIT haemorrhage has occurred, and therefore **stopping Clexane is most appropriate.**

**S**topping both anti-coagulation and anti-platelet medication together significantly increases the risk of in-stent thrombosis occurring.

**E**ven stopping one or both anti-platelet agents would carry an unacceptable level of risk so soon after PCI, and is therefore best avoided if possible.

# Acute coronary syndrome: initial management

**Acute coronary syndrome** (ACS) is a very common and important presentation in medicine. The management of ACS has evolved over recent years, with the development of new drugs and procedures such as percutaneous coronary intervention (PCI).

**Emergency departments** often have their own protocols based on local factors such as the availability of PCI and hospital drug formularies.
The following is based on the 2020 update to the NICE ACS guidelines.

### Acute coronary syndrome can be classified as follows:

- ST-elevation myocardial infarction (STEMI): ST-segment elevation + elevated biomarkers of myocardial damage
- non ST-elevation myocardial infarction (NSTEMI): ECG changes but no ST-segment elevation + elevated biomarkers of myocardial damage
- unstable angina

**The management of ACS depends on the particular subtype.**
**NICE management guidance groups the patients into two groups:**

1. STEMI
2. NSTEM/unstable angina

## For all patients with ACS

### Initial drug therapy

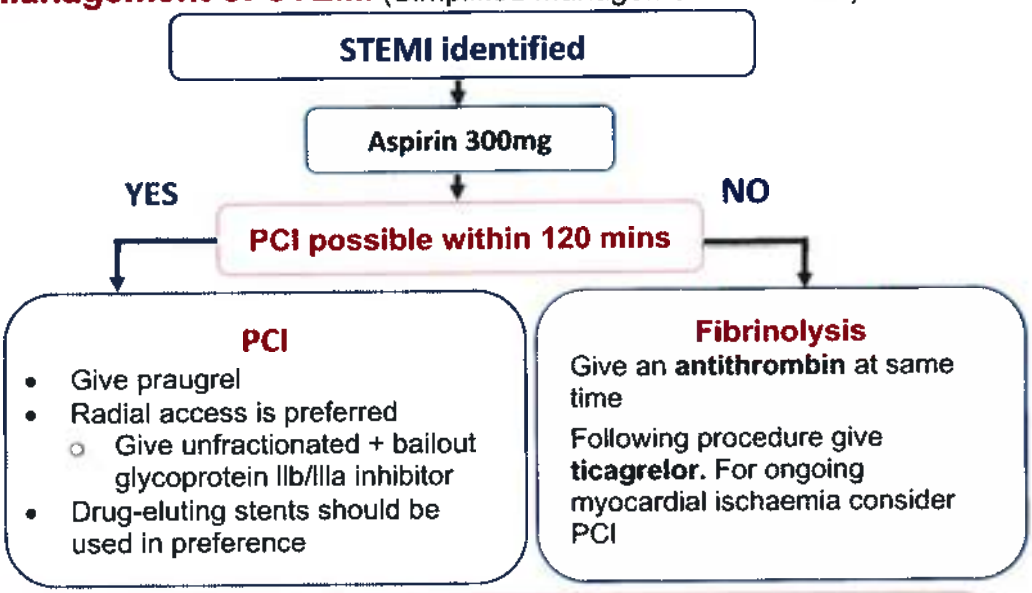
- aspirin 300mg
- oxygen should only be given if the patient has oxygen saturations < 94% in keeping with British Thoracic Society oxygen therapy guidelines
- morphine should only be given for patients with severe pain
  - previously IV morphine was given routinely
  - evidence, however, suggests that this may be associated with adverse outcomes
- nitrates
  - can be given either sublingually or intravenously
  - useful if the patient has ongoing chest pain or hypertension
  - should be used in caution if patient hypotensive

The next step in managing a patient with suspected ACS is to determine whether they meet the ECG criteria for STEMI.
It is, of course, important to recognise that these criteria should be interpreted in the context of the clinical history.

### STEMI criteria

- clinical symptoms consistent with ACS (generally of ≥ 20 minutes duration) with persistent (> 20 minutes) ECG features in ≥ 2 contiguous leads of:
  - 2.5 mm (i.e ≥ 2.5 small squares) ST elevation in leads V2-3 in men under 40 years, or ≥ 2.0 mm (i.e ≥ 2 small squares) ST elevation in leads V2-3 in men over 40 years
  - 1.5 mm ST elevation in V2-3 in women
  - 1 mm ST elevation in other leads
  - new LBBB (LBBB should be considered new unless there is evidence otherwise)

## Management of STEMI (Simplified Management of STEMI)




### Assumptions

- Patient presents within 12 hours of symptom onset
  - If patient Presents after 12 hours consider PCI if ongoing myocardial ischaemia or cardiogenic shock
- Patient is not a high bleeding risk
  - If patient is high bleeding risk consider swapping prasugrel for ticagrelor / swapping ticagrelor for clopidogrel
- Patient is not on oral anticoagulants
  - If patient is taking oral anticoagulants swap praugrel for dopidogrel

Diagram showing the simplified management of STEMI according to NICE guidelines. A number of assumptions (listed at the bottom) are made.

Once a STEMI has been confirmed the first step is to immediately assess eligibility for coronary reperfusion therapy. There are two types of coronary reperfusion therapy:

- **percutaneous coronary intervention**
  - should be offered if the presentation is within 12 hours of the onset of symptoms AND PCI can be delivered within 120 minutes of the time when fibrinolysis could have been given (i.e. consider fibrinolysis if there is a significant delay in being able to provide PCI)
  - if patients present after 12 hours and still have evidence of ongoing ischaemia then PCI should still be considered
  - drug-eluting stents are now used. Previously 'bare-metal' stents were sometimes used but have higher rates of restenosis
  - radial access is preferred to femoral access
- **fibrinolysis**
  - **should be offered within 12 hours of the onset of symptoms if primary PCI cannot be delivered within 120 minutes** of the time when fibrinolysis could have been given
  - a practical example may be a patient who presents with a STEMI to a small district general hospital (DGH) that does not have facilities for PCI. If they cannot be transferred to a larger hospital for PCI within 120 minutes then fibrinolysis should be given. If the patient's ECG taken 90 minutes after fibrinolysis failed to show resolution of the ST elevation then they would then require transfer for PCI

If patients are eligible this should be offered as soon as possible.

## Percutaneous coronary intervention for patients with STEMI

### Further antiplatelet prior to PCI

- this is termed 'dual antiplatelet therapy', i.e. aspirin + another drug
- if the patient is not taking an oral anticoagulant: prasugrel
- if taking an oral anticoagulant: clopidogrel

### Drug therapy during PCI

- patients undergoing PCI with radial access:
  - **unfractionated heparin with bailout glycoprotein IIb/IIIa inhibitor (GPI)** - this is the action of using a GPI during the procedure when it was not intended from the outset, e.g. because of worsening or persistent thrombus
- patients undergoing PCI with femoral access:
  - bivalirudin with bailout GPI

### Other procedures during PCI

- thrombus aspiration, but not mechanical thrombus extraction, should be considered
- complete revascularisation should be considered for patients with multivessel coronary artery disease without cardiogenic shock

## Fibrinolysis for patients with STEMI

Fibrinolysis used to be the only form of coronary reperfusion therapy available. However, it is used much less commonly now given the widespread availability of PCI.

The contraindications to fibrinolysis and other factors are described in other notes.

**Patients undergoing fibrinolysis should also be given an antithrombin drug.**

An ECG should be repeated after 60-90 minutes to see if the ECG changes have resolved. If patients have persistent myocardial ischaemia following fibrinolysis then PCI should be considered.

## Thrombolysis

ECG criteria for thrombolysis within 24 hours of typical pain include:

- **ST elevation** of more than **1 mm** in standard **limb** leads
- **ST elevation** more than **2 mm** in anterior **chest** leads, and
- **New left bundle branch block (LBBB).**

Thrombolytic drugs activate plasminogen to form plasmin. This in turn degrades fibrin and help breaks up thrombi. They in primarily used in patients with **STEMI.**

Other indications include **acute ischaemic stroke** and **acute pulmonary embolism with unstable haemodynamic**, although strict inclusion criteria apply.

### Examples:

- Streptokinase
- **Alteplase**
- Tenecteplase

### Contraindications to thrombolysis:

- **Active internal bleeding** (menses excluded).
- **GIT bleeding** within the **past month.**
- Coagulation and bleeding disorders.
- **Major trauma, major surgery or head injury within 3 wks.**

- Recent significant head injury
- **CNS neoplasm**
- **Previous haemorrhagic stroke at any time**
- **Ischaemic stroke < 3 months**
- Prolonged cardiopulmonary resuscitation (CPR) (> half an hour).
- Known or suspected **Aortic dissection**
- Pregnancy
- Severe uncontrolled hypertension
- **Proliferative** diabetic retinopathy: is **relative** contraindications.
- Allergy and oral anticoagulants: are **relative** contraindications.

Those patients over 75 years benefit from thrombolysis as much or more than younger patients with MI.

**Side-effects:**

- Haemorrhage
- Hypotension - more common with streptokinase
- Allergic reactions may occur with streptokinase

## Percutaneous coronary intervention (PCI)

Percutaneous coronary intervention (PCI) is a technique used to restore myocardial perfusion in patients with ischaemic heart disease, both in patients with stable angina and acute coronary syndromes.

**Stents are implanted in around 95% of patients** - it is now rare for just balloon angioplasty to be performed.

Following stent insertion migration and proliferation of smooth muscle cells and fibroblasts occur to the treated segment. The stent struts eventually become covered by endothelium. Until this happens there is an increased risk of platelet aggregation leading to thrombosis.

**Two main complications may occur:**

- **Stent thrombosis**: due to **platelet aggregation** as above. Occurs in **1-2%** of patients, most commonly **in the first month**. Usually presents with **acute myocardial infarction.**
- **In-stent Restenosis (ISRS)**: due to **excessive tissue proliferation** around stent. Occurs in around **5-20% of** patients, most commonly **in the first 3-6 months**. Usually presents with the **recurrence of angina symptoms**. Risk factors include **diabetes**, **renal** impairment and stents in venous bypass grafts.

**Types of stent:**

- Bare-metal stent **(BMS)**
- Drug-eluting stents **(DES):** stent coated with paclitaxel or rapamycin which inhibit local tissue growth. Whilst this reduces restenosis rates the stent thrombosis rates are increased as the process of stent endothelisation is slowed.

Following insertion, the most important factor in preventing stent thrombosis is **antiplatelet therapy**. **Aspirin** should be continued indefinitely.

The length of **clopidogrel** treatment depends on the type of stent, reason for insertion and consultant preference.

For Example: If patient has ectatic vessles the consultant may prefer to continue on clopidogrel.

Recently there is strong evidence that stop of aspirin and continue on clopidogrel is better for the stent survival.

## Laser trans-myocardial revascularisation

Open chest surgery is undertaken, during which **laser holes** are punched from the **epicardial** surface into areas of suspected ischaemic or hibernating ventricular muscle so **damages the endocardium**.

The process is not fully understood.

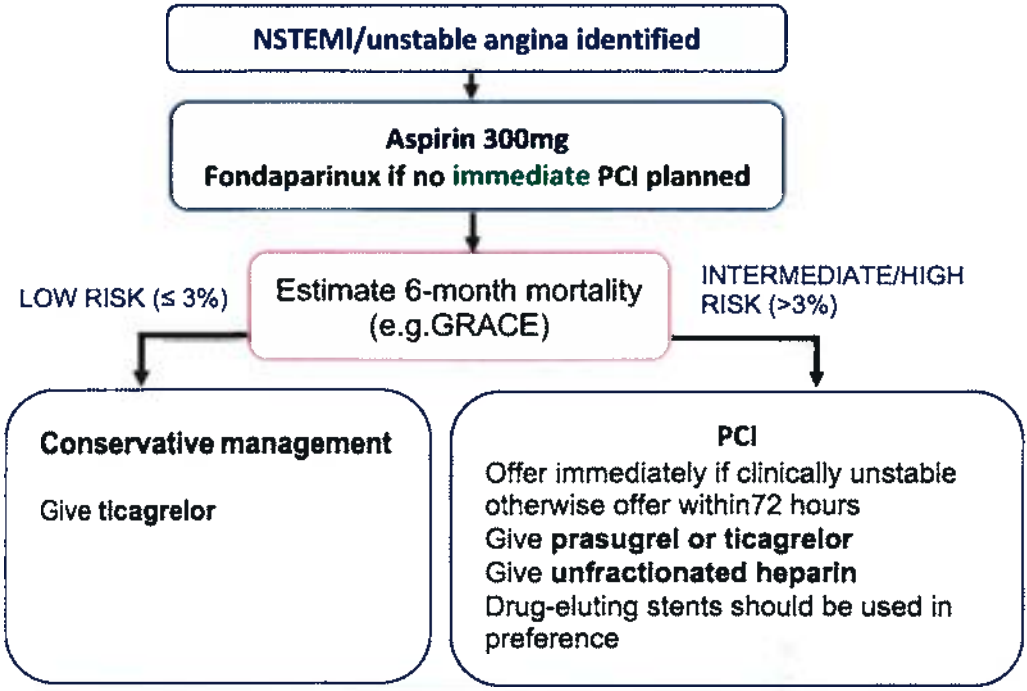
The epicardial end of the hole heals up leaving artificial channels communicating with the ventricular chamber and effectively forming new coronary vessels.

Laser trans-myocardial revascularisation has potential in **distal** disease as **DM**.

**Angioplasty** and **CABG** are useful in **proximal** disease.

## Management of NSTEMI/unstable angina

**Simplified management of NSTEMI/unstable angina**




**Assumptions**

- Patient is not a high bleeding risk. If patient is a high bleeding risk consider:
  - swapping Fondaparinux for an alternative antithrombin/dose
  - swapping prasugrel for ticagrelor / swapping ticagrelor for clopidogrel
- Patient is not on oral anticoagulants
  - If patient is taking oral anticoagulants swap praugrel/ticagrelor for clopidogrel

Diagram showing the simplified management of NSTEMI/unstable angina according to NICE guidelines. A number of assumptions (listed at the bottom) are made.

**The management** of NSTEMI/unstable angina is complicated and depends on individual patient factors and a **risk assessment.** The summary below provides an overview but the full NICE guidelines should be reviewed for further details.

### Further drug therapy

- antithrombin treatment
  - **fondaparinux** should be offered to patients who are not at a high risk of bleeding and who are not having angiography immediately
  - if immediate angiography is planned or a patients creatinine is > 265 µmol/L then unfractionated heparin should be given

## Risk assessment

The Global Registry of Acute Coronary Events (GRACE) is the most widely used tool for risk assessment and to decide upon further management.
In patient presents with an NSTEMI, If a patient is considered high-risk or is clinically unstable then coronary angiography will be performed during the admission.
Lower risk patients may have a coronary angiogram at a later date.
It can be calculated using online tools and takes into account the following factors:

- age
- heart rate, blood pressure
- cardiac (Killip class) and renal function (serum creatinine)
- cardiac arrest on presentation
- ECG findings
- troponin levels

This results in the patient being risk stratified as follows:

| Predicted 6-month mortality | Risk of future adverse cardiovascular events |
|---|---|
| 1.5% or below | Lowest |
| > 1.5% to 3.0% | Low |
| > 3.0% to 6.0% | Intermediate |
| > 6.0% to 9.0% | High |
| over 9.0% | Highest |

Based on **this risk assessment key decisions are made** regarding whether a patient has coronary angiography (with follow-on PCI if necessary) or has conservative management. The detailed pros/cons of this decision are beyond the scope of this book.

Which patients with NSTEMI/unstable angina should have coronary angiography (with follow-on PCI if necessary)?

- immediate: patient who are clinically unstable (e.g. hypotensive)
- **within 72 hours: patients with a GRACE score > 3%** i.e. those at intermediate, high or highest risk
- coronary angiography should also be considered for patients if ischemia is subsequently experienced after admission

### Further drug therapy

- unfractionated heparin should be given regardless of whether the patient has had fondaparinux or not
- further antiplatelet ('dual antiplatelet therapy', i.e. aspirin + another drug) prior to PCI
  - if the patient is not taking an oral anticoagulant: prasugrel or ticagrelor
  - if taking an oral anticoagulant: clopidogrel

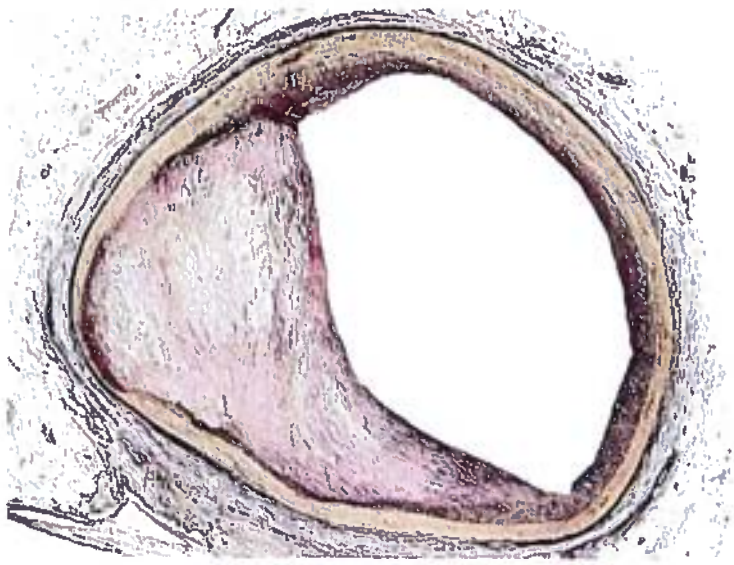
## Conservative management for patients with NSTEMI/unstable angina

### Further drug therapy

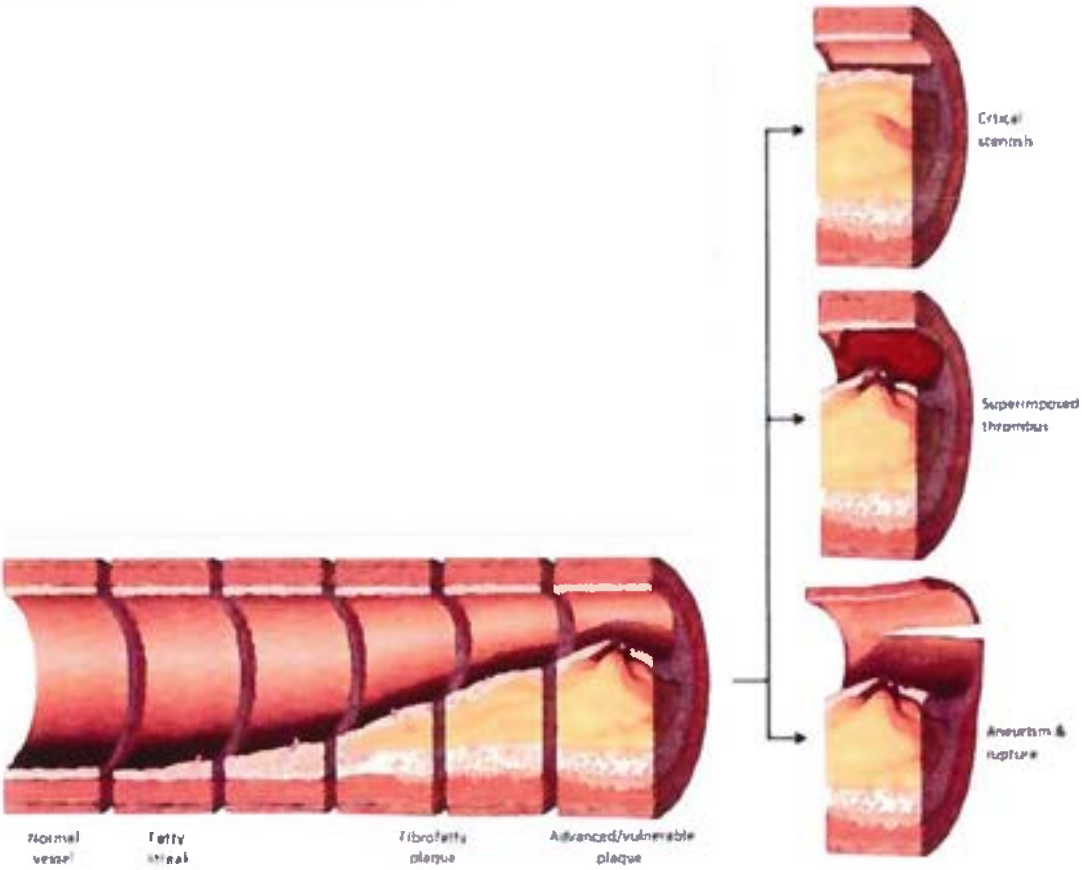
- further antiplatelet ('dual antiplatelet therapy', i.e. aspirin + another drug)
  - if the patient is not at a high risk of bleeding: ticagrelor
  - if the patient is at a high risk of bleeding: clopidogre

## Further images

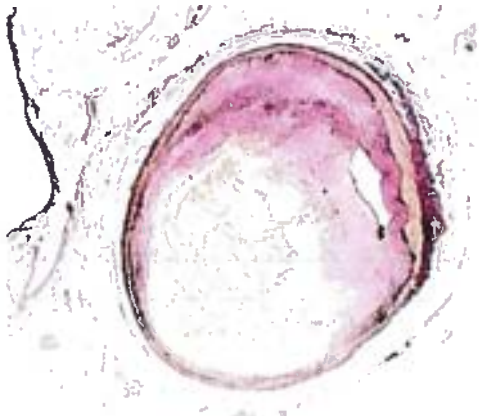
The following images show the progress of coronary artery atherosclerosis:



Slightly stenosed coronary artery



Moderately stenosed coronary artery, beetween 50-75%



Severely stenosed coronary artery

# Acute coronary syndrome: prognostic factors

Global Registry of Acute Coronary Events (GRACE) study has been used to derive regression models to predict death in hospital and death after discharge in patients with acute coronary syndrome

## Poor prognostic factors

- age
- development (or history) of heart failure
- peripheral vascular disease
- reduced systolic blood pressure
- Killip class*
- initial serum creatinine concentration
- elevated initial cardiac markers
- cardiac arrest on admission
- ST segment deviation

***Killip class** - system used to stratify risk post myocardial infarction

| Killip class | Features | 30-day mortality |
|---|---|---|
| I | No clinical signs heart failure | 6% |
| II | Lung crackles, S3 | 17% |
| III | Frank pulmonary oedema | 38% |
| IV | Cardiogenic shock | 81% |

ECG showing a ST elevation myocardial infarction (STEMI). Note by how looking at which leads are affected (in this case II, III and aVF) we are able to tell which coronary arteries are blocked (the right coronary artery in this case). A blockage of the left anterior descending (LAD) artery would cause elevation of V1-V4, what is often termed an 'anterior' myocardial infarction.

## Syndrome X

### Features

- angina-like chest pain on exertion
- ST depression on exercise stress test
- but **normal coronary arteries on angiography**

### Management

- nitrates may be beneficial

## Cardiac enzymes and biomarkers

Interpretation of the various cardiac enzymes has now largely been superceded by the introduction of troponin T and I. Questions still however commonly appear in exams.

### Key points for the exam:

- **Myoglobin** is the **first** to rise as early as **1 hr** of MI (within first 2 hrs), peak in 6-8 hrs and return to normal in 24 hr.
- **CK-MB** is useful to look for **re-infarction** as it returns to normal after 2-**3** days (troponin T remains elevated for up to 10 days).
- **GPBB** (Glycogen phosphorylase isoenzyme BB): is an isoenzyme of glycogen phosphorylase which exists in cardiac muscle. By **three hours post myocardial infarction** it has **risen significantly**. As such it is an **appropriate marker** for **early** cardiac muscle injury.

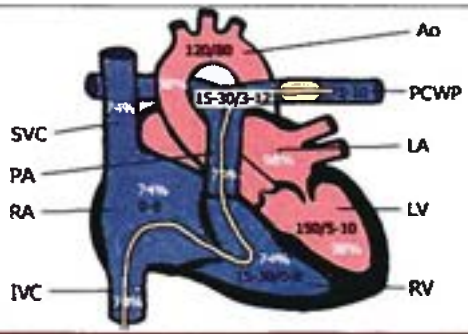
| | Begins to rise | Peak value | Returns to normal |
|---|---|---|---|
| **Myoglobin** | 1-2 hours | 6-8 hours | **1**-2 days |
| **CK-MB** | 2-6 hours | 16-20 hours | 2-**3** days |
| **CK** | 4-8 hours | 16-24 hours | 3-4 days |
| **Trop T** | 4-6 hours | 12-24 hours | 7-**10** days |
| **AST** | **12-24 hours** | 36-48 hours | 3-4 days |
| **LDH** | **24**-48 hours | 72 hours | 8-10 days |

**Troponin T** bind to **Tropomyosin** which is a protein which regulates actin. It associates with actin in muscle fibres and regulates muscle contraction by regulating the binding of myosin.

Troponin assay at **3** and **6 hours** is adequate to determine whether myocardial damage has occurred

## Causes of an elevated troponin are:

- Trauma
- Cardioversion
- Rhabdomyolysis
- Pulmonary embolism
- Pulmonary hypertension
- Hypertension
- Hypotension, especially with arrhythmias
- HOCM
- Myocarditis including Kawasaki's disease
- Sepsis
- Burns
- Subarachnoid haemorrhage and stroke
- Infiltrative/autoimmune disorders: including sarcoidosis, amyloidosis, haemochromatosis and scleroderma.
- **Drugs:** including **Adriamycin, Herceptin and 5-fluorouracil.**




Cardiac catheter data Normal cardiac pressures & oxygen saturation

| 11 | End systolic (mmHg) | End diastolic (mmHg) | Mean | O2 saturation |
|---|---|---|---|---|
| **Left heart** | | | | |
| Aorta | 120 | 80 | 95 | 98% |
| LV | 150 | 5-10 | | 98% |
| LA | | | | 98% |
| **Right heart** | | | | |
| RA | | | 0-8 | 74% |
| RV | 15-30 | 0-8 | | 74% |
| PA | 15-30 | 3-12 | 9-16 | 74% |
| SVC | | | | 74% |
| IVC | | | | 70% |
| PCWP | | | 1-10 | |

# Myocardial infarction: classification and management

## Myocardial infarction: new ESC 2020 classification:

### Type 1 myocardial infarction:

- **Type 1 myocardial infarction** is characterized by atherosclerotic plaque rupture,
- ulceration, fissure, or erosion with resulting in intraluminal thrombus in one or more coronary arteries leading to decreased myocardial blood flow and/or distal embolization and subsequent myocardial necrosis.
- The patient may have underlying severe coronary artery disease (CAD) but, on occasion (5-10% of cases), there may be non-obstructive coronary atherosclerosis or no angiographic evidence of CAD, particularly in women.

### Type 2 myocardial infarction

- **Type 2 MI is myocardial necrosis** in which a condition other than coronary plaque instability causes an imbalance between myocardial oxygen supply and demand. Mechanisms include hypotension, hypertension, tachyarrhythmias, bradyarrhythmia's, anemia, hypoxemia, but also by definition, coronary artery spasm, spontaneous coronary artery dissection (SCAD), coronary embolism, and coronary microvascular dysfunction.

### Types 3-5 myocardial infarction:

- The universal definition of MI also includes type MI (MI resulting in death when biomarkers are not available) and types 4 and 5 MI [related to PCI and coronary artery bypass grafting (CABG), respectively]

## Myocardial infarction: management

- **Management for people with STEMI not treated with PCI**
  Offer **ticagrelor**, as part of dual antiplatelet therapy with aspirin, to people with acute STEMI not treated with PCI, unless they have a high bleeding risk. [2020] .
- Consider **clopidogrel**, as part of dual antiplatelet therapy with aspirin, or aspirin alone, for people with acute STEMI not treated with PCI, if they have a high bleeding risk. [2020].
- Also see the NICE technology appraisal guidance on rivaroxaban for preventing adverse outcomes after management of acute coronary syndromes.
  Offer medical management to people with acute STEMI who are ineligible for any reperfusion therapy.

## NICE suggest the following in terms of oxygen therapy:

**Do not routinely administer oxygen**, but monitor oxygen saturation using pulse oximetry as soon as possible, ideally before hospital admission. Only offer supplemental oxygen to:

- People with oxygen saturation **(SpO2) of less than 94%** who are not at risk of hypercapnic respiratory failure, **aiming for SpO2 of 94-98%**
- People with COPD who are at risk of hypercapnic respiratory failure, to achieve a **target SpO2 of 88-92%** until blood gas analysis is available.

Primary percutaneous coronary intervention (**PCI**) has emerged as **the gold-standard treatment for STEM**I but is not available in all centres.
Thrombolysis should be performed in patients without access to primary PCI.

**With regards to thrombolysis:**

- Tissue plasminogen activator **(tPA)** has been shown to offer clear mortality benefits over streptokinase.
- Tenecteplase is easier to administer and has been shown to have non-inferior efficacy to alteplase with a similar adverse effect profile.

An **ECG should be performed 90 minutes following thrombolysis** to assess whether there has been **a greater than 50% resolution in the ST elevation.**

- If there has not been adequate resolution then **rescue PCI** is superior to repeat thrombolysis.
- For patients successfully treated with thrombolysis, **PCI** has been shown to be beneficial. The optimal timing of this is still under investigation.

In pt. with STEMI due to; **Cocaine** which is a drug of widespread abuse and remains one of the commonest causes of acute MI in men **below 35 years of age**. Cocaine-induced MI is thought to be related to **coronary artery spasm** as many patients do not have overt coronary artery disease. It is probably caused by stimulation of the α-adrenergic receptors in smooth muscle cells. In addition, cocaine increases endothelin-1 (a VC) and decreases nitric oxide (VD).
Consequently guidelines suggest the use of **IV nitrates (GTN)** in the **first** instance coupled with **calcium antagonists**. **Benzodiazepines IV** are also effective in resolving chest pain and improving cardiac performance. If there is no improvement in the clinical condition, **then angiography** should be considered. **Thrombolytic are generally avoided.**

Also, it is important to **avoid beta-blockers** in treating cocaine-induced chest pains or acute MI, as this may result in unopposed alpha 1 adrenergic action with worsening coronary spasm.

# Myocardial infarction: secondary prevention

NICE produced guidelines on the management of patients following a MI in 2020. Some key points are listed below:

## All patients should be offered the following drugs:

- **ACE inhibitor.**
- **Aspirin.**
- **Beta-blocker.**
- **Statin.**

**Clopidogrel**:

- Since Clopidogrel is very potent antiplatelets drug it is now much more widely used post-MI and randomized controlled studies recommend its use after the first year and to stop aspirin .
- STEMI: the European Society of Cardiology recommend **dual antiplatelets** for **12 months**. In UK (aspirin + Clopidogrel).
- NSTEMI: following the 2020 NICE unstable angina and NSTEMI guidelines **clopidogrel** should be given for the first **12 months if the 6 month mortality risk is > 1.5%** (this "The 6 month mortality" may be calculated using a validated risk model such as GRACE).
- The AHA/ACC/SCAI/ACS/ADA published recommendations in 2020 stressed the **importance of 12 months of dual antiplatelet therapy** after **placement of a drug-eluting stent (DES).**
- For people already on anticoagulation who have had PCI, continue anticoagulation and clopidogrel for up to 12 months. If the person is taking a direct oral anticoagulant, adjust the dose according to bleeding risk, thromboembolic risk and cardiovascular risk
- For people with a new indication for anticoagulation who have had PCI, offer clopidogrel (to replace prasugrel or ticagrelor) for up to 12 months and an oral anticoagulant licensed for the indication, which best matches the person's:
- bleeding risk Acute coronary syndromes (NG185) thromboembolic risk
- cardiovascular risk
- wishes. [2020]
- For people already on anticoagulation, or those with a new indication, who have not had PCI (medical management, CABG), continue anticoagulation and, unless there is a high risk of bleeding, consider continuing aspirin (or clopidogrel for people with contraindication for aspirin) for up to 12 months. [2020] .
- Do not routinely offer prasugrel or ticagrelor in combination with an anticoagulant that is needed for an ongoing separate indication for anticoagulation. [2020]

- For people with an ongoing indication for anticoagulation 12 months after an MI, take into consideration all of the following when thinking about the need for continuing antiplatelet therapy:
- indication for anticoagulation
- bleeding risk
- thromboembolic risk
- cardiovascular risk
- person's wishes.
- **Even you should postpone any elective operations rather than to stop the dual antiplatelet therapy.**

### Aldosterone antagonists:

- Patients who have had an acute MI and who have symptoms and/or signs of heart failure and left ventricular systolic dysfunction, treatment with an aldosterone antagonist licensed for post-MI treatment (e.g., eplerenone)
- should be initiated within 3-14 days of the MI, preferably after ACE inhibitor therapy.

Any Pt. Post MI= ACEI + βB + ASA + Plavix + Statins ± Aldactone

NICE guidelines on **MI: secondary prevention (CG48)** recommend a number of lifestyle modifications as prevention. These include **increasing physical activity** to **20-30 minutes per day**.

## Myocardial infarction: complications

Patients are at risk of a number of immediate, early and late complications following a myocardial infarction (MI).

### Cardiac arrest:

This most commonly occurs due to patients developing **ventricular fibrillation (VF)** and is the **most common cause of death following a MI**. Patients are managed as per the ALS protocol with defibrillation.

### Cardiogenic shock:

If a large part of the ventricular myocardium is damaged in the infarction the ejection fraction of the heart may decrease to the point that the patient develops cardiogenic shock (=biventricular failure with low BP). This is **difficult to treat**. Other causes of cardiogenic shock include the 'mechanical' complications such as left ventricular free wall rupture as listed below.

In cardiogenic shock >>> **cardiac index below 2 L/min/m2**

Patients may require **inotropic (Dopamine)** support and/or an **Intra-Aortic Balloon Counter Pulsation (IABCP).**

Cardiogenic shock >> **ATN** >> acute renal failure (type 1 cardiorenal syndrome).

## Treatment of cardiogenic shock (APO) as by AHA-ACLS:

### First step:

- High flow O2
- Lasix 1mg/kg IV
- Morphine 2-4 mg IV
- GTN SL

### Second step (guide by SBP):

- SBP > 100 mmHg >>> **GTN IVI** 10-20 Mcg/min.
- SBP 70-100 mmHg with No signs or symptoms of shock >>> **Dobutamine** IVI 2-20 Mcg/kg/min.
- SBP 70-100 mmHg with signs or symptoms of shock >>> **Dopamine** IVI 5-15 Mcg/kg/min.
- SBP < 70 mmHg with signs or symptoms of shock >>> **Noradrenaline** IVI 0.5-30 Mcg/min

Crucial to prognosis is haemodynamic stabilisation, and in this case with hypotension and shock, **IABCP to support cardiac output is the best approach**.

Balloon inflation is timed with **diastole; once closure of the aortic valve** has occurred; this corresponds to the **middle of the T wave**. For blood to be ejected antegrade to perfuse the tissues and retrograde to perfuse the coronaries the aortic valve must be closed and competent.

**Aortic regurgitation** is therefore a **contraindication** to placement of an intra-aortic balloon pump.

Inotropes such as adrenaline and noradrenaline can significantly increase myocardial ischaemia, as such they would only be adjunctive support after IABCP.

Whilst vasodilators such as GTN can significantly improve myocardial blood flow, they are inappropriate here because of hypotension.

## Chronic heart failure:

As described above, if the patient survives the acute phase their ventricular myocardium may be dysfunctional resulting in chronic heart failure. Loop diuretics such as **furosemide** will decrease fluid overload. **Both ACE-inhibitors and beta-blockers** have been shown to improve the long-term prognosis of patients with chronic heart failure.

## Tachy-arrhythmias:

Ventricular fibrillation, as mentioned above, is the most common cause of death following a MI. Other common arrhythmias including ventricular tachycardia.

**Post MI ventricular tachycardia (VT)** is most commonly due to **scar** tissue. It may also be related to ischaemia.

The definitive investigation would be **Electrophysiological study EPS** due to the fact that if this were **scar-related VT** the site could be localised and even possibly **ablated**. If not, then an implantable cardio-defibrillator (**ICD**) implantation may be considered.

The development of VT/VF in the **first** day following an acute MI >>> is thought to be of **no prognostic significance** if dealt with promptly either by DC or medically by amiodarone 200 mg 1x3.

However, the **late** development of VT/VF in the context of a full thickness myocardial scar, as evidenced by **Q waves** on the ECG, carries **a very poor prognosis**. And so **ICD** has been shown to offer improved survival over anti-arrhythmic therapy. **Amiodarone** would be an appropriate choice in patients who are **unsuitable for ICD insertion.**

The development of late onset VT following an ischaemic event (Acute MI) coupled with LV impairment on echo >>> is an indication for ICD.

**EX**: Pt with MI and developed a broad spectrum tachycardia **after 1 month** of MI with Q waves in ECG >>> **Treatment** is **ICD**, not amiodarone tab

## Brady arrhythmias:

Atrioventricular block is more common following **inferior** MI.

## Pericarditis:

Pericarditis in the **first 48 hours** following a **large transmural MI** is common (c. 10% of patients).

The pain is typical for pericarditis (worse on lying flat, radiation to the **trapezius** edge etc.), a pericardial friction rub may be heard and a pericardial effusion may be demonstrated with an echocardiogram.

It is usually managed by **increase aspirin to 650 mg every 4 hr** and analgesia like paracetamol.

Anticoagulant **can be continued** if there is no pericardial effusion, as in such cases the risk of haemorrhagic pericarditis is low. However in the presence of significant effusion or if the effusion is increasing, heparin/LMWL should be discontinued.

**Dressler's syndrome:** tends to occur **around 2-6 weeks following a MI.** The underlying pathophysiology is thought to be an **autoimmune** reaction against antigenic proteins formed as the myocardium recovers. It is characterised by a combination of fever, pleuritic pain, pneumonitis, pericardial effusion and a **raised ESR.** It is treated with **aspirin in large**

**doses** or **NSAIDs** not steroid. If recurrent colchicine can be used, **pericardiocentesis** can be required in rare cases.

**ECG:** tall R in V1 and V2.
**CXR:** Cardiomegaly ± pleural effusion

**Cardiac tamponade:** is a known complication of acute MI, the clue of diagnosis is **sudden onset dyspnoea** with **clear lung fields**, **cardiogenic shock** and **electrical alternans**, consistent with **ventricular rupture.**
**Treatment:** the definitive Treatment is **pericardiocentesis** with emergency ventricular repair, if haemodynamically unstable >>> **IV Inotropes** + arrange for insertion of **IABP** (Intra-aortic balloon pump) + **colloids** to establish the patient before pericardiocentesis takes place.

## Left ventricular aneurysm:

The ischaemic damage sustained may weaken the myocardium resulting in aneurysm formation. This is typically associated with **persistent ST elevation** and left ventricular failure. Thrombus may form within the aneurysm increasing the risk of stroke. Patients are therefore **anticoagulated.**

## Left ventricular free wall rupture:

This is seen in around 3% of MIs and occurs around 1-2 weeks afterwards. Patients present with acute heart failure secondary to **cardiac tamponade** (**raised JVP**, pulsus paradoxus, diminished heart sounds). Urgent pericardiocentesis and thoracotomy are required.

## Ventricular septal rupture:

Rupture of the interventricular septum usually occurs in the **first week** and is seen in around **1-2%** of patients. The average time from MI to rupture has been reported to be between 2 and 4 days, but it may be as short as a **few hours** or as long as 2 weeks. It occurs most commonly after **anterior MI.** Features: **acute heart failure with low BP and tachycardia** associated with **a pan-systolic murmur**. An **echocardiogram** is diagnostic and will exclude acute mitral regurgitation which presents in a similar fashion. **Mortality is very high**. **Urgent surgical correction** is needed.

## Acute mitral regurgitation:

More common with **infero-posterior** infarction and may be due to ischaemia or **rupture of the papillary muscle**. An early-to-mid **systolic** murmur is typically heard radiated into the axilla with **associated pulmonary oedema** due to **mitral valve prolapse**. Patients are treated with vasodilator therapy like ACEI and diuretics but often require **emergency surgical repair**.

Pt with **MI >>> suddenly develops pulmonary oedema** and a **loud systolic murmur** >>> this is due to **acute left ventricular failure (LVF)** with mitral valve prolapse (MVP) ± ventricular septal defect (VSD). >>> So do **Right heart catheterisation and oximetry.**

**NB**: The post-MI ventricular septal defect (VSD) or post-MI rupture of papillary muscle (causing acute mitral regurgitation).

VSD and papillary rupture are difficult to distinguish clinically. The diagnosis is established by **demonstration of a left to right shunt.**

The presence of a **VSD** would be confirmed by **detecting a step-up in the oxygen saturation between the RA and PA**; if there is no step-up, the diagnosis is probably papillary muscle rupture.

**NB**: The most specific finding for a diagnosis of myocardial infarction is >> **Evolution of Q waves on ECG.**

- **The evolution of Q waves** is the most suggestive of an infarct. A Q wave is any negative deflection that precedes an R wave on the ECG. Small Q-waves are normal in most leads, and they can be prominent in leads III and aVR as a normal variant, but should not be seen in leads V1-V3. They are considered **pathological** if they are **more than 1mm wide, more than 2mm deep, more than 25% of the depth of the QRS complex, or seen in leads V1-V3.** Such pathological Q-waves usually indicate prior full thickness myocardial infarct.
- **Cardiac enzymes** may be elevated in pulmonary embolism (PE), renal failure and sepsis. It is increasingly recognised that raised troponin is not specific to myocardial ischaemia, and therefore must be interpreted in the context of the clinical history.
- **Raised ST segments** can be associated with conditions such as pericarditis, and is again not specific for myocardial ischaemia.
- As any medical doctor on call knows, **severe chest pain** has a vast number of differential diagnoses.
- **Akinetic wall motion on the echo** may occur with any regional disease process like amyloid, etc.

# Peripheral arterial disease

## Peripheral arterial disease: Management

Peripheral arterial disease (PAD) is strongly linked to smoking. Patients who still smoke should be given help to **quit smoking**.

**Comorbidities should be treated**, including

- hypertension
- diabetes mellitus
- obesity

As with any patient who has established cardiovascular disease, all patients should be taking a **statin**. Atorvastatin 80 mg is currently recommended. In 2010 NICE published guidance suggesting that **clopidogrel** should be used first-line in patients with peripheral arterial disease in preference to aspirin.

**Exercise training** has been shown to have significant benefits. NICE recommend a supervised exercise programme for all patients with peripheral arterial disease prior to other interventions.

**Severe PAD or critical limb ischaemia may be treated by:**

- **endovascular revascularization**
  - percutaenous transluminal angioplasty +/- stent placement
  - endovascular techniques are typically used for short segment stenosis (e.g. < 10 cm), aortic iliac disease and high-risk patients
- **surgical revascularization**
  - surgical bypass with an autologous vein or prosthetic material
  - endarterectomy
  - open surgical techniques are typically used for long segment lesions (> 10 cm), multifocal lesions, lesions of the common femoral artery and purely infrapopliteal disease

Amputation should be reserved for patients with critical limb ischaemia who are not suitable for other interventions such as angioplasty of bypass surgery.

**Drugs licensed for use in peripheral arterial disease (PAD) include:**

- **naftidrofuryl oxalate**: vasodilator, sometimes used for patients with a poor quality of life
- **cilostazol:** phosphodiesterase III inhibitor with both antiplatelet and vasodilator effects - not recommended by NICE

# Renal vascular disease

Renal vascular disease is most commonly due to **atherosclerosis** (> 95% of patients).

It is associated with risk factors such as **smoking** and **hypertension** that cause atheroma elsewhere in the body.

It may present as hypertension, chronic renal failure or **'flash' pulmonary oedema.**

In younger patients however fibromuscular dysplasia **(FMD)** needs to be considered.

FMD is more common in **young women** and characteristically has a **'string of beads'** appearance on angiography.

Patients respond well to **balloon angioplasty**

## Investigation:

- **MRA angiography** is now the investigation of choice
- CT angiography
- Conventional renal angiography is less commonly performed used nowadays, but may still have a role when planning surgery.

# Pulmonary Hypertension

## Primary Pulmonary Hypertension (PPH)

The classification of pulmonary hypertension is currently changing with the term **idiopathic pulmonary arterial hypertension (IPAH)** becoming more widely used.

**Primary pulmonary hypertension (PPH, now IPAH):**

- Pulmonary arterial pressure **> 25 mmHg at rest, > 30 mmHg with exercise** (The normal value is 14 mmHg).
- PPH is diagnosed when no underlying cause can be found
- Around 10% of cases are familial: **autosomal dominant**
- Endothelin thought to play a key role in pathogenesis
- **Associated with HIV, cocaine** and **weight reduction drugs (e.g. fenfluramine).**
- There is **an average delay about 2 years** between onset of symptoms and diagnosis by which time corpulmonale has usually developed

### Features:

- More common in **females,** typically presents at **20-40 years** old
- Often presents in women **after the birth of the first child.**
- **Progressive SOB**
- Cyanosis
- Right ventricular heave, loud P2, raised JVP with prominent 'a' waves, tricuspid regurgitation.

**Young female + increased SOB and recurrent syncope >> PPH**

### Investigation:

- Echocardiography: increased right sided pressures, RV enlargement.
- **V/Q scan**: may shows patchy filling defects different from those seen in PE, so V/Q scan remains part of the diagnostic work up of PH.
- Acute vasoreactivity test.
- **Cardiac catheterisation:** ↑ PASP

**NB:** Whilst echocardiography may strongly point towards a **diagnosis** of pulmonary hypertension, all patients need to have right heart pressures measured. **Cardiac catheterisation** is therefore **the single most important investigation** to **confirm** the diagnosis of pulmonary hypertension.

## Management:

- **Diuretics** if right heart failure
- Anticoagulation
- Vasodilator therapy:
  - **Endothelin-1 receptor antagonist: Bosentan**
  - **IV prostaglandins,**
  - CCB, are effective in only 10-15% of patients and only recommended **if there is no right sided heart failure**.
- Heart-lung transplant

**NB**: **Pregnant** females with **pulmonary hypertension:**

- Have a high mortality of at least **30%** - some authors put it at **50%** - seemingly highest immediately after delivery.
- Therefore, the patient **should be advised about the risk to her own health of continuing with the pregnancy versus considering a termination of pregnancy.**
- Patient who are against termination of pregnancy should be closely followed up and managed with **heparin**, **oxygen** and **pulmonary vasodilator therapy like prostacyclin.**
- **Bosentan is teratogenic and should not be used in pregnancy.**

The patient should be advised for **contraception** in future, but oral contraceptive pills should not be used for possible increased risk of thrombois

# Pulmonary arterial hypertension (PAH):

## Features and management:

Pulmonary arterial hypertension (PAH) may be defined as a sustained elevation in **mean** pulmonary arterial pressure of **greater than 25 mmHg at rest** or **30 mmHg after exercise.** Around 10% of cases are inherited in an autosomal dominant fashion.

## Pulmonary capillary wedge pressure

Pulmonary capillary wedge pressure (PCWP) is measured using a balloon tipped Swan-Ganz catheter which is inserted into the pulmonary artery. The pressure measured is similar to that of the left atrium (normally 6-12 mmHg).

One of the main uses of measuring the PCWP is determining whether pulmonary oedema is caused by either heart failure or acute respiratory distress syndrome.

In many modern ITU departments PCWP measurement has been replaced by non-invasive techniques.

## PAH has recently been reclassified by the WHO into 5 groups:

**Group 1: Pulmonary arterial hypertension (PAH):**

- **Idiopathic (IPAH)** (previously termed primary pulmonary hypertension).
- **Familial.**
- Associated conditions: **collagen** vascular disease, congenital heart disease with systemic to pulmonary shunts, HIV, sickle cell disease, systemic sclerosis and drugs, toxins.
- Persistent pulmonary hypertension of the new born.

**Group 2: Pulmonary venous hypertension with left heart disease:**
**Left-sided** atrial, ventricular or valvular disease such as left ventricular systolic and diastolic dysfunction, mitral stenosis, mitral regurgitation, fibrosing mediastinitis and **vaso-occulsive disease**.

Pulmonary venous hypertension with increased left atrial pressure is most commonly caused by left ventricular dysfunction as in congestive cardiac failure, which causes an elevation in PA pressure by increased back-pressure through the lungs.

**Group 3: Pulmonary hypertension secondary to lung disease/hypoxia:**

- COPD
- Interstitial lung disease (ILD)
- Sleep apnoea
- High altitude

**Group 4: Pulmonary hypertension due to thromboembolic disease:**
**Group 5: Miscellaneous conditions:**

- lymphangiomatosis e.g., secondary to carcinomatosis or **sarcoidosis**

## Features:

- **Exertional dyspnoea** is the most frequent symptom
- Chest pain and **syncope** may also occur
- **Loud P2**
- **Left parasternal heave** (due to right ventricular hypertrophy)

**Management:** should first involve **treating any underlying conditions,** for example with anticoagulants or oxygen.

Following this, it has now been shown that **acute vasodilator testing** is central **to deciding on the appropriate management strategy.**

**Acute vasodilator testing** aims to decide which patients show a significant fall in pulmonary arterial pressure following the administration of vasodilators such as **IV Epoprostenol** or **inhaled nitric oxide.**

**If there is a positive response to acute vasodilator testing:**

- **Oral calcium channel blockers.**

**If there is a negative response to acute vasodilator testing:**

- **Endothelin receptor antagonists**: **Bosentan** and ambrisentan (They significantly reduce pulmonary artery pressure, but adverse effects include peripheral oedema and LFTs monitoring is recommended).
- **Prostacyclin analogues: iloprost**, treprostinil
- **Phosphodiesterase- 5 (PDE-5) inhibitors:** sildenafil

# Pulmonary embolism

## Pulmonary embolism: investigation

### Investigation:

We know from experience that few patients (around 10%) present with the textbook triad of pleuritic chest pain, dyspnoea and haemoptysis. Pulmonary embolism can be difficult to diagnose as it can present with virtually any cardiorespiratory symptom/sign depending on its location and size.

### So which features make pulmonary embolism more likely?

The PIOPED study[1] in 2007 looked at the frequency of different symptoms and signs in patients who were diagnosed with pulmonary embolism.

**The relative frequency of common clinical signs is shown below:**

- Tachypnea (respiratory rate >20/min) - 96%
- Crackles - 58%
- Tachycardia (heart rate >100/min) - 44%
- Fever (temperature >37.8°C) - 43%

It is interesting to note that the Well's criteria for diagnosing a PE use tachycardia rather than tachypnoea.

All patients with symptoms or signs suggestive of a PE should have a history taken, examination performed and a chest x-ray to exclude other pathology.

### Pulmonary embolism rule-out criteria (PERC)

**NICE updated** their guidelines on the investigation and management of venous thromboembolism (VTE) in 2020. One of the key changes was the use of the pulmonary embolism rule-out criteria (the **PERC** rule)

- a copy of criteria can be found in the image below
- **all** the criteria must be absent to have negative PERC result, i.e. rule-out PE
- this should be done when you think there is a low pre-test probability of PE, but want more reassurance that it isn't the diagnosis
  - this low probability is defined as < 15%, although it is clearly difficult to quantify such judgements
- a negative PERC reduces the probability of PE to < 2%
- if your suspicion of PE is greater than this then you should move straight to the 2-level PE Wells score, without doing a PERC

## Pulmonary embolism rule-out criteria (PERC)

| Criteria |
|---|
| **Age ≥ 50** |
| **Heart rate ≥ 100** |
| **Oxygen saturations ≤ 94%** |
| **Previous DVT or PE** |
| **Recent surgery or trauma in the past 4 weeks** |
| **Haemoptysis** |
| **Unilateral leg swelling** |
| **Oestrogen use (e.g. HRT, contraceptives)** |
| **If all of the above are absent the post-test probability of PE is < 2%** |

## 2-level PE Wells score

If a PE is suspected a 2-level PE Wells score should be performed:

| Clinical feature | Points |
|---|---|
| Clinical signs and symptoms of DVT (minimum of leg swelling and pain with palpation of the deep veins) | 3 |
| An alternative diagnosis is less likely than PE | 3 |
| Heart rate > 100 beats per minute | 1.5 |
| Immobilisation for more than 3 days or surgery in the previous 4 weeks | 1.5 |
| Previous DVT/PE | 1.5 |
| Haemoptysis | 1 |
| Malignancy (on treatment, treated in the last 6 months, or palliative) | 1 |

### Clinical probability simplified scores

- PE likely - more than 4 points
- PE unlikely - 4 points or less

### If a PE is 'likely' (more than 4 points)

- arrange an immediate **computed tomography pulmonary angiogram (CTPA)**
- If there is a delay in getting the CTPA then interim therapeutic anticoagulation should be given until the scan is performed.
  - interim therapeutic anticoagulation used to mean giving low-molecular-weight heparin
  - NICE updated their guidance in 2020. They now recommend using an anticoagulant that can be continued if the result is positive.
  - this means normally a direct oral anticoagulant (DOAC) such as apixaban or rivaroxaban

- if the CTPA is positive then a PE is diagnosed
- if the CTPA is negative then consider a proximal leg vein ultrasound scan if DVT is suspected

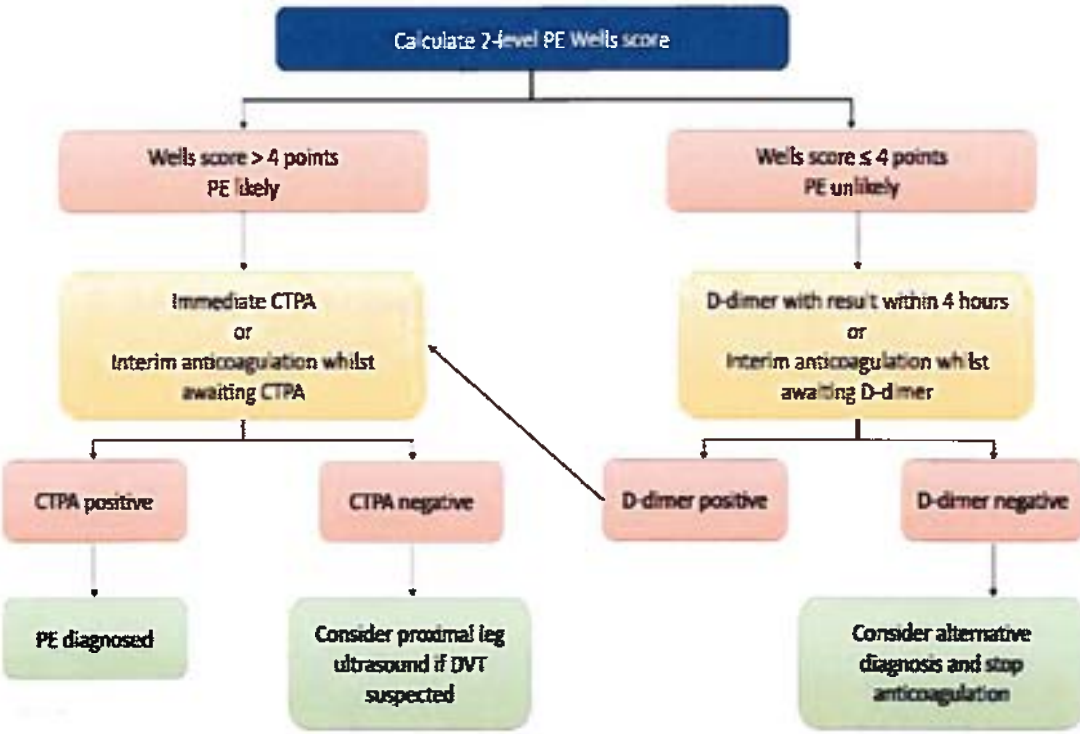
**If a PE is 'unlikely' (4 points or less)**

- **arranged a D-dimer test**
  - if positive arrange an immediate computed tomography pulmonary angiogram (CTPA). If there is a delay in getting the CTPA then give interim therapeutic anticoagulation until the scan is performed
  - if negative then PE is unlikely - stop anticoagulation and consider an alternative diagnosis

## 2- level PE wells test

| Criteria | Points |
|---|---|
| Clinical signs and symptoms of DVT (minimum of leg swelling and pain with palpation of the deep veins) | 3 |
| An alternative diagnosis is less likely than PE | 3 |
| Heart rate > 100 | 1.5 |
| Immobilisation for more than 3 days or surgery in the previous 4 weeks | 1.5 |
| Previous DVT/PE | 1.5 |
| Haemoptysis | 1 |
| Malignancy (on treatment, treated in the last 6 months, or palliative) | 1 |

**Score > 4 points PE likely**
**Score ≤ 4 points PE unlikely**




## CTPA or V/Q scan?

The consensus view from the British Thoracic Society and NICE guidelines is as follows:

- **CTPA is now the recommended initial lung-imaging modality for non-massive PE.** Advantages compared to V/Q scans include speed, easier to perform out-of-hours, a reduced need for further imaging and the possibility of providing an alternative diagnosis if PE is excluded
- if the CTPA is negative then patients do not need further investigations or treatment for PE
- V/Q scanning may be used initially if appropriate facilities exist, the chest x-ray is normal, and there is no significant symptomatic concurrent cardiopulmonary disease. V/Q scanning is also the investigation of choice if there is **renal impairment** (doesn't require the use of contrast unlike CTPA)

## Some other points

### D-dimers

- sensitivity = 95-98%, but poor specificity
- age-adjusted D-dimer levels should be considered for patients > 50 years

### ECG

- the classic ECG changes seen in PE are a large S wave in lead I, a large Q wave in lead III and an inverted T wave in lead III - 'S1Q3T3'. However, this change is seen in no more than 20% of patients
- right bundle branch block and right axis deviation are also associated with PE
- sinus tachycardia may also be seen

### Chest x-ray

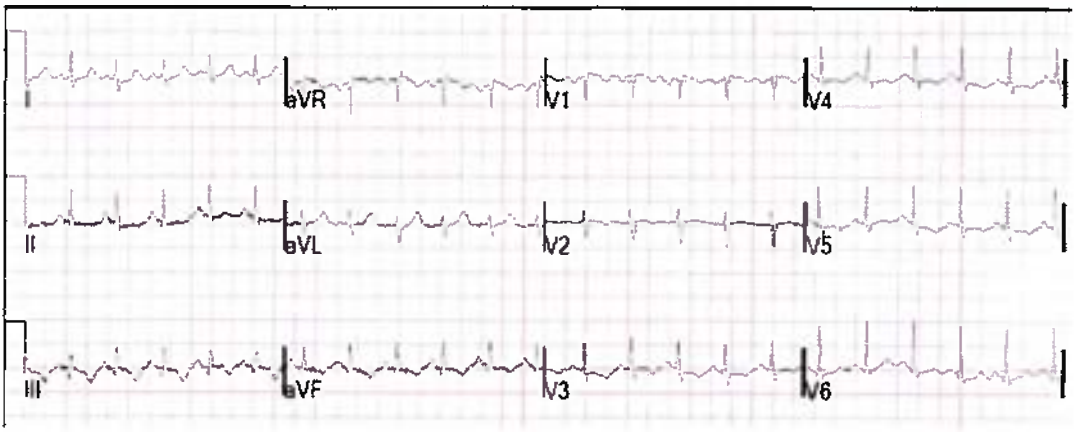
- a chest x-ray is recommended for all patients to exclude other pathology
- however, it is typically **normal in PE**
- possible findings include a wedge-shaped opacification

### V/Q scan

- sensitivity of around 75% and specificity of 97%
- other causes of mismatch in V/Q include old pulmonary embolisms, AV malformations, vasculitis, previous radiotherapy
- COPD gives matched defects

### CTPA

- peripheral emboli affecting subsegmental arteries may be missed




Clinical Characteristics of Patients with Acute Pulmonary Embolism(Data from PIOPED II)

## Pulmonary embolism: management

NICE updated their guidelines on the management of venous thromboembolism (VTE) in 2020.
Some of the key changes include recommending the following:

- the use of direct oral anticoagulants (DOACs) as first-line treatment for most people with VTE
- the use of DOACs in patients with active cancer, as opposed to low-molecular weight heparin as was the previous recommendation
- outpatient treatment in low-risk pulmonary embolism (PE) patients
- routine cancer screening is no longer recommended following a VTE diagnosis

### Outpatient treatment in low-risk PE patients

Deep vein thrombosis has for a long time been treated on an outpatient condition. In contrast, patients with any form of PE were typically admitted. However, in recent years patients with a new diagnosis of PE who are deemed low-risk are now increasingly managed as outpatients. NICE formally supported this approach in their latest guidance.

- NICE recommends using a 'validated risk stratification tool' to determine the suitability of outpatient treatment.
  - no guidance is given as to what tool should be used
  - the 2018 British Society guidelines support the use of the Pulmonary Embolism Severity Index (PESI) score
- key requirements would clearly be haemodynamic stability, lack of comorbidities and support at home

## Anticogulant therapy

The cornerstone of VTE management is anticoagulant therapy.
This was historically done with warfarin, often preceded by heparin until the INR was stable. However, the development of DOACs, and an evidence base supporting their efficacy, has changed modern management.

### Choice of anticoagulant

- the big change in the 2020 guidelines was the increased use of DOACs
- apixaban or rivaroxaban (both DOACs) should be offered first-line following the diagnosis of a PE
  - instead of using low-molecular weight heparin (LMWH) until the diagnosis is confirmed, NICE now advocate using **a DOAC once a diagnosis is suspected,** with this continued if the diagnosis is confirmed
  - if neither apixaban or rivaroxaban are suitable then either LMWH followed by dabigatran or edoxaban OR LMWH followed by a vitamin K antagonist (VKA, i.e. warfarin)
- if the patient has active cancer
  - previously LMWH was recommended
  - the new guidelines now recommend using a DOAC, unless this is contraindicated
- if renal impairment is severe (e.g. < 15/min) then LMWH, unfractionated heparin or LMWH followed by a VKA
- if the patient has antiphospholipid syndrome (specifically 'triple positive' in the guidance) then LMWH followed by a VKA should be used

### Length of anticoagulation

- all patients should have anticoagulation for at least 3 months
- continuing anticoagulation after this period is partly determined by whether the VTE was provoked or unprovoked
  - a provoked VTE is due to an obvious precipitating event e.g. immobilisation following major surgery. The implication is that this event was transient and the patient is no longer at increased risk
  - an unprovoked VTE occurs in the absence of an obvious precipitating event, i.e. there is a possibility that there are unknown factors (e.g. mild thrombophilia) making the patient more at risk from further clots
- **if the VTE was provoked the treatment is typically stopped after the initial 3 months** (3 to 6 months for people with active cancer)

- **if the VTE was unprovoked then treatment is typically continued for up to 3 further months (i.e. 6 months in total)**
  - NICE recommend that whether a patient has a total of 3-6 months anticoagulant is based upon balancing a person's risk of VTE recurrence and their risk of bleeding
  - the HAS-BLED score can be used to help assess the risk of bleeding
  - NICE state: '*Explain to people with unprovoked DVT or PE and a low bleeding risk that the benefits of continuing anticoagulation treatment are likely to outweigh the risks.* '. The implication of this is that in the absence of a bleeding risk factors, patients are generally better off continuing anticoagulation for a total of 6 months

## PE with haemodynamic instability

### Thrombolysis

- thrombolysis is now recommended as the first-line treatment for massive PE where there is circulatory failure (e.g. hypotension)
- other invasive approaches should be considered where appropriate facilities exist

Patients who have repeat pulmonary embolisms, despite adequate anticoagulation, may be **considered for inferior vena cava (IVC) filters.** These work by stopping clots formed in the deep veins of the leg from moving to the pulmonary arteries.
IVC filter use is currently supported by NICE but other studies suggest a weak evidence base - please see the link for more details.

## Pregnancy: DVT/PE investigation

Guidelines were updated by the Royal College of Obstetricians.

### For patients with a suspected deep vein thrombosis (DVT):

- Compression duplex ultrasound should be undertaken where there is clinical suspicion of DVT

### For patients with a suspected pulmonary embolism (PE):

- ECG and chest x-ray should be performed in all patients
- In women who also have symptoms and signs of DVT, compression duplex ultrasound should be performed. If compression ultrasonography confirms the presence of DVT, no further investigation is necessary and treatment for VTE should continue
- the decision to perform a V/Q or CTPA should be taken at a local level after discussion with the patient and radiologist

## Comparing CTPA to V/Q scanning in pregnancy

| CTPA | V/Q scanning |
|---|---|
| CTPA slightly increases the lifetime risk of **maternal breast cancer** (increased by up to 13.6%, background risk of 1/200 for study population). Pregnancy makes breast tissue particularly sensitive to the effects of radiation | V/Q scanning carries a slightly increased risk of **childhood cancer** compared with CTPA (1/50,000 versus less than 1/1,000,000) |

D-dimer is of limited use in the investigation of thromboembolism as it often raised in pregnancy.

# Cardiac imaging

## Cardiac imaging

### non-invasive techniques excluding echocardiography

The ability to image the heart using non-invasive techniques such as MRI, CT and radionuclides has evolved rapidly over recent years.

### Nuclear imaging:

These techniques use radiotracers which are extracted by normal myocardium. Examples include:

- **Thallium**
- **Technetium (99mTc) SestaMIBI:** a coordination complex of the radioisotope technetium-99m with the ligand methoxyisobutyl isonitrile (MIBI), used in 'MIBI' or cardiac Single Photon Emission Computed Tomography (SPECT) scans
- **Fluorodeoxyglucose (FDG):** used in Positron Emission Tomography (**PET**) scans

The primary role of SPECT is to assess **myocardial perfusion and myocardial viability.**

**Two** sets of images are usually acquired. First the myocardium at **rest** followed by images of the myocardium during **stress** (either exercise or following adenosine / dipyridamole).

By comparing the rest with stress images any areas of ischaemia can classified as **reversible or fixed** (e.g. following a myocardial infarction). Cardiac PET is predominately a research tool at the current time.

**MUGA:**

- Multi Gated Acquisition Scan, also known as radionuclide angiography
- Radionuclide (technetium-99m) is injected IV.
- The patient is placed under a **gamma camera**
- May be performed as a stress test
- It can accurately **measure left ventricular ejection fraction (LVEF). Typically used before and after cardiotoxic drugs are used in cancer patients.**

## Cardiac Computed Tomography (CT):

Cardiac CT is useful for assessing suspected ischaemic heart disease, using two main methods:

- **Calcium score:** there is known to be a correlation between the amount of atherosclerotic plaque calcium and the risk of future ischaemic events. Cardiac CT scan quantify the amount of calcium producing a 'calcium score'.
- **Contrast enhanced CT**: allows visualisation of the coronary artery lumen.

If these two techniques are combined cardiac CT has a very high negative predictive value for ischaemic heart disease.

## Cardiac MRI:

Cardiac MRI (commonly termed CMR) has become the gold standard for providing **structural** images of the heart. It is particularly useful when assessing **congenital** heart disease, determining right and left ventricular mass and differentiating forms of **cardiomyopathy**. Myocardial perfusion can also be assessed following the administration of gadolinium. Currently CMR provides limited data on the extent of coronary artery disease.

# Cardiac catherization and oxygen saturation levels

Questions regarding cardiac catherization and oxygen saturation levels can seem daunting at first but a few simple rules combined with logical deduction can usual produce the answer.

## Let's start with the basics:

- Deoxygenated blood returns to the right side of the heart via the superior vena cava (SVC) and inferior vena cava (IVC). It has an oxygen saturation level of around **70%**. The right atrium (RA), right ventricle (RV) and pulmonary artery (PA) normally have oxygen saturation levels of around **70%**

- The lungs oxygenate the blood to a level of around **98-100%**. The left atrium (LA), left ventricle (LV) and aorta should all therefore have oxygen saturation levels of 98-100%

## Some examples:

| Diagnosis & notes | RA | RV | PA | LA | LV | Aorta |
|---|---|---|---|---|---|---|
| **Normal** | **70%** | **70%** | **70%** | **100%** | **100%** | **100%** |
| **Atrial septal defect (ASD)**<br>The oxygenated blood in the LA mixes with the deoxygenated blood in the RA, resulting in intermediate levels of oxygenation from the RA onwards | **85%** | **85%** | **85%** | **100%** | **100%** | **100%** |
| **Ventricular septal defect (VSD)**<br>The oxygenated blood in the LV mixes with the deoxygenated blood in the RV, resulting in intermediate levels of oxygenation from the RV onwards. The RA blood remains deoxygenated | **70%** | **85%** | **85%** | **100%** | **100%** | **100%** |
| **Patent ductus arteriosus (PDA)**<br>Remember, a PDA connects the higher-pressure aorta with the lower pressure PA. This results in only the PDA having intermediate oxygenation levels | **70%** | **70%** | **85%** | **100%** | **100%** | **100%** |
| **VSD with Eisenmenger's** | **70%** | **70%** | **70%** | **100%** | **85%** | **85%** |
| **PDA with Eisenmenger's** | **70%** | **70%** | **70%** | **100%** | **100%** | **85%** |
| **ASD with Eisenmenger's** | **70%** | **70%** | **70%** | **85%** | **85%** | **85%** |

# Cardiomyopathies

## Cardiomyopathy

### key points

The old classification of dilated, restricted and hypertrophic cardiomyopathy has been largely abandoned due to the high degree of overlap. The latest classification of cardiomyopathy by the WHO and American Heart Association reflect this.

The tables below shows a very limited set of exam related facts for the various cardiomyopathies:

**Primary cardiomyopathies** - predominately involving the heart

**Genetic** - both conditions listed below are autosomal dominant. An implantable cardioverter-defibrillator is often inserted to reduce the incidence of sudden cardiac death.

| Type of cardiomyopathy | Selected points |
|---|---|
| **Hypertrophic obstructive cardiomyopathy** | **Leading cause of sudden cardiac death in young athletes**<br>Usually due to a mutation in the gene encoding β-myosin heavy chain protein<br>Common cause of sudden death<br>**Echo findings include MR, systolic anterior motion (SAM) of the anterior mitral valve and asymmetric septal hypertrophy** |
| **Arrhythmogenic right ventricular dysplasia** | **Right ventricular myocardium is replaced by fatty and fibrofatty tissue**<br>**Around 50% of patients have a mutation of one of the several genes which encode components of desmosome**<br>ECG abnormalities in V1-3, typically T wave inversion.<br>An **epsilon wave** is found in about 50% of those with ARV - this is best described as a terminal notch in the QRS complex |

**Mixed** - rather confusingly most of the causes of dilated and restrictive cardiomyopathy are now listed separately in the 'secondary' causes. This category servers as a reminder that many patients will have a genetic predisposition to cardiomyopathy which is then triggered by the secondary process, hence the 'mixed' category

| Type of cardiomyopathy | Selected causes/points |
|---|---|
| **Dilated cardiomyopathy** | **Classic causes include**<br>• alcohol<br>• Coxsackie B virus<br>• wet beri beri<br>• doxorubicin |
| **Restrictive cardiomyopathy** | **Classic causes include**<br>• amyloidosis<br>• post-radiotherapy<br>• Loeffler's endocarditis |

| Type of cardiomyopathy | Selected points |
|---|---|
| **Peripartum cardiomyopathy** | Typical develops between last month of pregnancy and 5 months post-partum<br>More common in older women, greater parity and multiple gestations |
| **Takotsubo cardiomyopathy** | 'Stress'-induced cardiomyopathy e.g. patient just found out family member dies then develops chest pain and features of heart failure<br>**Transient, apical ballooning of the myocardium**<br>Treatment is supportive |

## Acquired

**Secondary cardiomyopathies**- pathological myocardial involvement as part of a generalized systemic disorder

| Type of cardiomyopathy | Selected causes/points |
|---|---|
| **Infective** | Coxsackie B virus<br>Chagas disease |
| **Infiltrative** | Amyloidosis |
| **Storage** | Haemochromatosis |
| **Toxicity** | **Doxorubicin**<br>Alcoholic cardiomyopathy |
| **Inflammatory (granulomatous)** | Sarcoidosis |
| **Endocrine** | Diabetes mellitus<br>Thyrotoxicosis<br>Acromegaly |
| **Neuromuscular** | Friedreich's ataxia<br>Duchenne-Becker muscular dystrophy<br>Myotonic dystrophy |
| **Nutritional deficiencies** | Beriberi (thiamine) |
| **Autoimmune** | Systemic lupus erythematosis |

Cardiac amyloidosis most commonly presents as restrictive cardiomyopathy. The clinical findings are those of right heart failure ie jugular venous distension and peripheral oedema, whereas orthopnoea and paroxysmal nocturnal dyspnoea are typically absent in more advanced stages systolic dysfunction also occurs. Postural hypotension can occur as result of poor ventricular filling or associated autonomic neuropathy. Combination of low voltage electrocardiogram (ECC) and thickened ventricular walls is one of the characteristic features of cardiac amyloidosis. Other echocardiographic abnormalities include dilatation of atria, thickened interatrial septum. diastolic dysfunction and small-volume Ventricles. The most distinctive feature of cardiac amyloidosis is a sparkling. granular appearance of the myocardium, but this is a relatively insensitive feature occurring only in about 25% of cases Cardiac amyloidosis usually occurs in setting of light chain amyloidosis (AL) and hereditary amyloidosis and rarely in secondary amyloidosis

Haemochromatosis and sarcoidosis can also cause restrictive cardiomyopathy but the combination of ventricular wall thickness and low-voltage ECG make the diagnosis of cardiac amyloidosis more likely

Echocardiography in ischaemic cardiomyopathy usually reveals systolic dysfunction and regional wall motion abnormalities

Diabetic nephropathy does not explain the electrocardiographic and echocardiographic findings in this Patient.

# Dilated cardiomyopathy (DCM)

Dilated cardiomyopathy (DCM) is the **most common form of cardiomyopathy**, accounting for 90% of cases.

## Causes:

- idiopathic: the most common cause
- myocarditis: e.g. **Coxsackie B**, HIV, diphtheria, **Chagas disease**
- ischaemic heart disease
- peripartum
- hypertension
- iatrogenic: e.g. **doxorubicin**
- substance abuse: e.g. **alcohol, cocaine**
- inherited: either a familial genetic predisposition to DCM or a specific syndrome e.g. **Duchenne muscular dystrophy**
  - around a third of patients with DCM are thought to have a genetic predisposition
  - a large number of heterogeneous defects have been identified
  - the majority of defects are inherited in an autosomal dominant fashion although other patterns of inheritance are seen
- infiltrative e.g. haemochromatosis, sarcoidosis + these causes may also lead to restrictive cardiomyopathy
- nutritional e.g. wet beriberi (thiamine deficiency)

## Pathophysiology

- Dilated heart leading to systolic (+/- diastolic) dysfunction
- **All 4 chambers** affected **but LV more so than RV**
- Features include arrhythmias, emboli, **mitral regurgitation (NOT AR)**
- Absence of congenital, valvular or ischaemic heart disease

## Features

- classic findings of heart failure
- systolic murmur: stretching of the valves may result in mitral and tricuspid regurgitation
- **S3**
- **'balloon' appearance of the heart on the chest x-ray**

**NB**: - Haemochromatosis is more commonly associated with restrictive cardiomyopathy but a dilated pattern may also be seen.

- There is a known association between Wilson's disease and cardiomyopathy but this is extremely rare and not often clinically significant.

- The indications of **anticoagulant** in patient with **heart failure low EF%** especially in those who have:
  1) A previous thrombo-embolic event
  2) Intracardiac thrombus.
  3) LV aneurysm.

**Treatment** of DCM: Lasix + Aldactone ± HCZ + ACEI + Carvedilol + Lanoxin + Statin + ASA ± Plavix ± Warfarin.

**NB:** RALES (Randomised Aldactone Evaluation Study) showed that **aldactone in a small dose of 25 mg** reduced mortality by **30%** when added to conventional therapy of CHF

**NB**: Patients with ICM with recurrent refractory HF although medical ttt >>> **Heart transplantation**, although **LVAD (Lt Ventricular Assisted Device)** may be used but **not currently supported in UK** due to lack of RCT evidence, there are **some interventional clinical trials have been carried out**, (**REMATCH trial**), The Randomized Evaluation of Mechanical Assistance Therapy as an alternative in Congestive Heart Failure.

## Hypertrophic Obstructive Cardiomyopathy (HOCM)

**HOCM** is an **autosomal dominant** disorder of muscle tissue caused by defects in the genes encoding contractile proteins.

**The** estimated prevalence is **1 in 500**.

**HOCM** is **the most common cause** of sudden cardiac death in the **young.**

### Pathophysiology

- The most common defects involve a mutation in the gene encoding **β-myosin heavy chain protein** or myosin binding protein C.
- Mutations to various proteins including alpha-tropomyosin and troponin T have been identified.
- results in predominantly diastolic dysfunction
  - left ventricle hypertrophy → decreased compliance → decreased cardiac output
- characterized by myofibrillar hypertrophy with chaotic and disorganized fashion myocytes ('disarray') and fibrosis on biopsy

The history of sudden arrhythmia and death in a **young**, **previously well**, individual is suggestive of HOCM. Relatives should be screened for it.

## Features:

- often asymptomatic
- exertional dyspnoea
- angina
- **syncope**
  - typically following exercise
  - due to subaortic hypertrophy of the ventricular septum, resulting in functional aortic stenosis
- **sudden death** (most commonly due to **ventricular arrhythmias**), arrhythmias, heart failure
- jerky pulse, large 'a' waves, double apex beat
- ejection systolic murmur
  - increases with Valsalva manoeuvre and decreases on squatting
  - hypertrophic cardiomyopathy may impair mitral valve closure, thus causing regurgitation

## Associations:

- Friedreich's ataxia
- Wolff-Parkinson White

## Echo - mnemonic - **MR SAM ASH**

- Mitral regurgitation (MR)
- Systolic anterior motion (SAM) of the anterior mitral valve leaflet
- Asymmetric hypertrophy (ASH): concentric hypertrophy (undilated) LV (increased septal versus LV wall diameter of ratio of > 1.3:1).

## ECG:

- **RBBB**,
- **Prolonged PR,**
- **Non-specific T wave abnormalities.**
- **LVH**
- Deep **Q waves** in anterolateral and inferior leads
- AF may occasionally be seen

## Cardiac catheterisation:

- Left ventricular pressures are high (210/15) with a steep drop-off between the LV and aortic systolic pressures (125/75).

ECG showing typical changes of HOCM including LVH and T wave inversion.

This young male patient was shown to have HOCM. Note the LVH and deep ST depression and T-wave inversion.

## Poor prognostic factors (6):

1) **Syncope.**
2) **Young** age at presentation.
3) **Family history of HOCM and sudden death.**
4) **Non-sustained ventricular tachycardia** on 24 or 48-hr Holter monitoring.
5) **Abnormal blood pressure changes on exercise** (drop of BP during peak exercise on stress testing).
6) An increased **septal wall thickness > 3 cm:** Septal hypertrophy causes left ventricular outflow **(LVOT)** obstruction. It is an important cause of sudden death in apparently healthy individuals.

## Management (ABCDE):

- **Amiodarone.**
- **B**eta-blockers or verapamil for symptoms
- **Cardioverter defibrillator (ICD).**
- **D**ual chamber pacemaker.
- **E**ndocarditis prophylaxis*

**N.B:** Reducing outflow tract obstruction with **myomectomy** or alcohol septal ablation does **not** reduce the risk of sudden cardiac death **(SCD),** but it is usually recommended especially when the **outflow gradient is greater than 50 mmHg particularly if symptoms of dyspnoea persist post β blockade.**

**Drugs to avoid:**

- **Nitrates.**
- **ACE-inhibitors.**
- **Inotropes.**

**NB:** Verapamil should however be avoided in HOCM patients with coexistent Wolff-Parkinson White as it may precipitate VT or VF.

**NB:** Most cardiologists would now proceed to inserting an implantable cardioverter defibrillator (ICD) to lower the risk of sudden cardiac death **(SCD).**

**Example:** Patient with HOCM with palpitations , a 24 hour ECG reveals runs of non-sustained VT .Best treatment is **ICD.**

**NB: The most common causes of sudden cardiac death (SCD):**

- **HOCM** is a **more common** cause of sudden cardiac death than arrhythmogenic right ventricular dysplasia (ARVD). The estimated prevalence is **1 in 500.**
- **ARVC** (Arrhythmogenic right ventricular cardiomyopathy): the **second** most common cause of sudden cardiac death in the young after HOCM.
- **CPVT** (Catecholaminergic polymorphic ventricular tachycardia) is a form of inherited cardiac disease. It is inherited in an autosomal dominant fashion and has a prevalence of **around 1:10,000.**
- **Brugada syndrome** is a form of inherited cardiovascular disease. It is inherited in an autosomal dominant fashion and has an estimated prevalence of **1:5,000-10,000.** Brugada syndrome is more common in **Asians.**

## Screening of HOCM:

Current guidelines suggest that a **resting ECG** and **TTE (transthoracic ECHO)** are the **most effective** screening strategies for relatives of patients with HOCM.

**Genetic** testing is **not** recommended as a first line screening tool given varying rates of penetrance.

## Restrictive cardiomyopathy

### Causes

- amyloidosis (e.g. secondary to myeloma) - most common cause in UK
- haemochromatosis
- post-radiation fibrosis
- Loffler's syndrome: endomyocardial fibrosis with a prominent eosinophilic infiltrate
- endocardial fibroelastosis: thick fibroelastic tissue forms in the endocardium; most commonly seen in young children
- sarcoidosis
- scleroderma

### Pathophysiology

- primarily characterized by decreased compliance of the ventricular endomyocardium
- causes predominately diastolic dysfunction

### Features

- similar to constrictive pericarditis
- low-voltage ECG

**Features suggesting restrictive cardiomyopathy rather than constrictive pericarditis**

- prominent apical pulse
- absence of pericardial calcification on CXR
- the heart may be enlarged
- ECG abnormalities e.g. bundle branch block, Q waves

### Investigations

- echocardiography
- cardiac MRI

## Takotsubo cardiomyopathy

Takotsubo cardiomyopathy is a type of non-ischaemic cardiomyopathy associated with a transient, apical ballooning of the myocardium. It may be triggered by stress.

### Pathophysiology:

- Takotsubo is a Japanese word that describes an octopus trap

- the apical ballooning appearance occurs due to severe hypokinesis of the mid and apical segments with preservation of activity of the basal segments. In simple terms, the bottom of the heart (the apex) does not contract and therefore appears to balloon out. However, the area closer to the top (the base) continues to contract (creating the neck of the octopus trap)

### Features:

- chest pain
- features of heart failure
- ECG: ST-elevation
- normal coronary angiogram

### Treatment is supportive.

### Prognosis:

- the majority of patients improve with supportive treatment

## Fabry disease

**Fabry disease** is an **X linked recessive** condition due to a deficiency of the enzyme alpha-galactosidase A which results in the accumulation of a glycolipid within the endothelium resulting in abnormalities of the skin, eye, kidneys and neurological systems.

The responsible gene is located on the long arm of the X chromosome.

**The diagnosis** is confirmed by demonstration of **absent or deficient levels of alpha-galactosidase A** in leucocytes, plasma or cultured fibroblasts.

An X linked recessively inherited condition can exist in **female carriers** who may exhibit mild to moderate symptoms. This is due to variable expression according to random X inactivation of the affected gene in embryogenesis and explains the presence of mild disease in this patient's sister.

### The disorder has three distinct clinical entities:

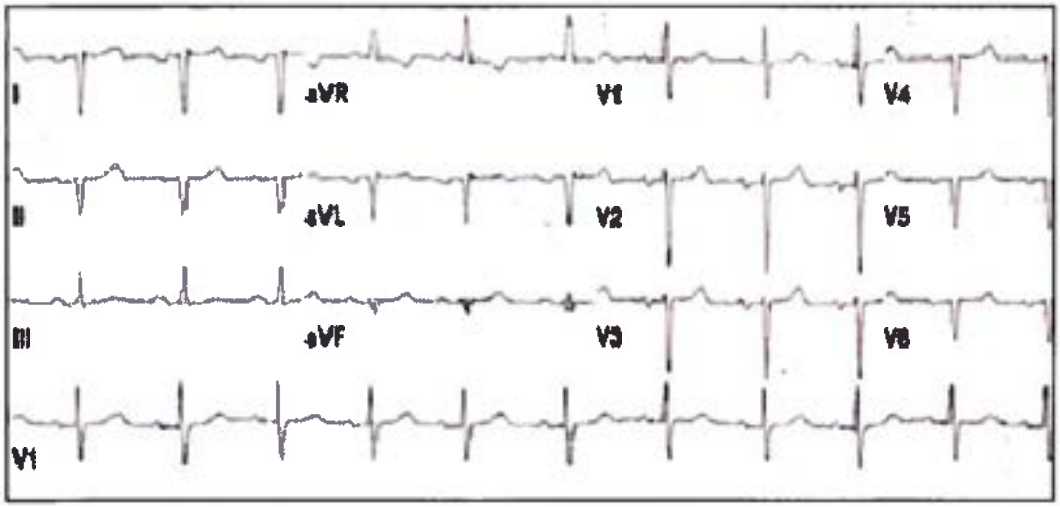
1) Classical presentation in the male homozygote with early presentation in childhood - angiokeratomas, heart failure, cataracts and renal disease.
2) Male homozygotes with atypical presentation in adulthood with proteinuria, Acro-paraesthesia (hand and foot disease), angiokeratomas and cardiomegaly.
3) Female heterozygotes can present again in adulthood with similar mild symptoms.

# Congenital heart disease

## Dextrocardia

**Dextrocardia >>> characteristic ECG features are:**

- Inverted P waves with negative QRS deflection in **lead I**,
- Upright P waves with a positive QRS deflection in lead **aVR** with mirror image finding in lead **aVL**.
- A shift of the P axis (usually about + 120 degrees) and
- Reversed R wave progression through chest leads V1 to V6.




Dextrocardia may be associated with **Kartagener's** syndrome which is dextrocardia + bronchiectasis + chronic sinusitis + immotile cilia infertility.

Dextrocardia may be alone or associated with **situs inversus totalis**, so should do both **CXR** and **abdomen US**.

# Congenital heart disease: types

**Acyanotic** - most common causes

- Ventricular septal defects **(VSD)** - **most common**, accounts for **30%**
- Atrial septal defect **(ASD)**: 10%
- Patent ductus arteriosus (PDA)
- **Coarctation of the aorta**
- **Aortic valve stenosis**

**VSDs** are more common than ASDs. However, in adult patients ASDs are the more common new diagnosis as they generally presents later.

**Cyanotic** - most common causes:

- Tetralogy of Fallot **(F4)**
- Transposition of the great arteries **(TGA)**
- **Tricuspid atresia (NOT mitral atresia)**
- Pulmonary valve stenosis
- **Total anomalous pulmonary venous connection** (TAPVC): consists of an abnormality of blood flow in which all four pulmonary veins drain into systemic veins or the right atrium with or without pulmonary venous obstruction i.e. systemic and pulmonary venous blood mix in the RA.

**Fallot's is more common than TGA**. However, **at birth TGA is the more common** lesion as patients with Fallot's generally presenting at around 1-2 months following the identification of a murmur or cyanosis.

TGA is the most common presenting cause of cyanotic congenital heart disease.

**Congenital heart disease:**

- **Acyanotic**: **VSD** most common cause
- **Cyanotic**: **TGA** most common **at birth, Fallot's most common overall**

**N.B:**

- **Aortic regurgitation** may be a feature of **osteogenesis imperfecta( MCQ)**

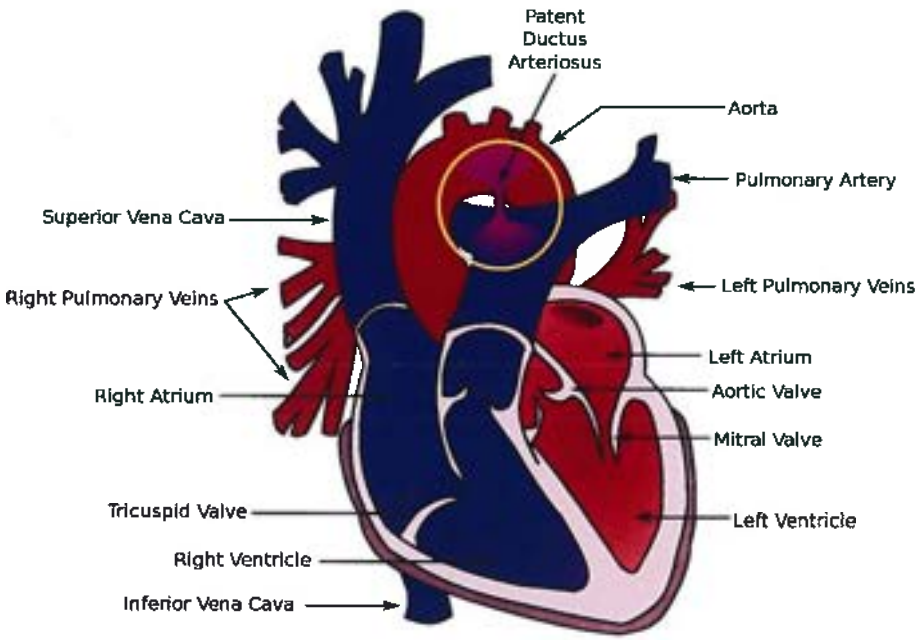
- The majority of cases of **neonates** with **complete heart block** (? neonatal lupus) may be caused by **autoimmune** disease, particularly **anti-Ro antibodies** in the **mother who has SLE during the pregnancy**.

- **Left ventricle (LV) hypoplasia** occurs when the **left** sided chambers **fail** to **develop** and blood enters the systemic circulation from the right ventricle via the pulmonary artery and a patent ductus arteriosus.

# Patent ductus arteriosus (PDA)

## Overview:

- a form of congenital heart defect
- generally classed as 'acyanotic'. However, uncorrected can eventually result in late cyanosis in the lower extremities, termed differential cyanosis
- connection between the pulmonary trunk and descending aorta
- usually, the ductus arteriosus closes with the first breaths due to increased pulmonary flow which enhances prostaglandins clearance
- more common in premature babies, born at high altitude or maternal rubella infection in the first trimester




## Features:

- **Left subclavicular thrill.**
- **Continuous 'machinery' murmur**. But when the shunt **reverses** (as in patients with a large PDA and/or pulmonary disease) the murmur becomes **softer** and **shorter**.
- Large volume, bounding, **collapsing pulse.**
- **Wide pulse pressure.**
- **Heaving apex beat.**

### Management:

- **indomethacin or ibuprofen**
  - given to the neonate
  - inhibits prostaglandin synthesis
  - closes the connection in the majority of cases
- if associated with another congenital heart defect amenable to surgery then prostaglandin E1 is useful to keep the duct open until after surgical repair

## Ventricular septal defects (VSD)

Ventricular septal defects (VSD) are the most common cause of congenital heart disease. They close spontaneously in around 50% of cases.

### Aetiology

- congenital VSDs are often association with chromosomal disorders
  - Down's syndrome
  - Edward's syndrome
  - Patau syndrome
  - cri-du-chat syndrome
- congenital infections
- acquired causes
  - post-myocardial infarction

VSDs may be detected in utero during the routine 20 week scan. Post-natal presentations include:

- failure to thrive
- features of heart failure
  - hepatomegaly
  - tachypnoea
  - tachycardia
  - pallor
- classically a pan-systolic murmur which is louder in smaller defects

### Management is clearly highly specialised

- small VSDs which are asymptomatic often close spontaneously are simply require monitoring
- moderate to large VSDs usually result in a degree of heart failure in the first few months
  - nutritional support
  - medication for heart failure e.g. diuretics
  - surgical closure of the defect

## Complications:

- aortic regurgitation
  - aortic regurgitation is due to a poorly supported right coronary cusp resulting in cusp prolapse
- infective endocarditis
- Eisenmenger's complex
  - due to prolonged pulmonary hypertension from the left-to-right shunt
  - results in right ventricular hypertrophy and increased right ventricular pressure. This eventually exceeds the left centricular pressure resulting in reversal of blood flow
  - this is turn results in cyanosis and clubbing
  - Eisenmenger's complex is an indication for a heart-lung transplant
- right heart failure
- pulmonary hypertension
  - pregnancy is contraindicated in women with pulmonary hypertension as it carries a 30-50% risk of mortality

# Atrial septal defects (ASD)

ASD is often first diagnosed in adulthood and represents **30% of all adult** congenital heart disease.

**Female**: male ratio is **3:1** and **75%** of them are ASD **ostium secondum**.

Communications at the level of the atria allows left-to-right shunting of blood, leading to considerable increase in right-heart output >> lead to **pulmonary hypertension**.

**Fixed splitting of S2** on auscultation and **mild systolic murmur** over P area.

ECG >>> **RBBB** ± Rt axis deviation

Patients often present with **AF**.

CXR >>> **pulmonary plethora**

Significant ASD should be repaired below the age of 10 years or as soon as possible if diagnosed in adulthood.

**Transoesophageal echo (TEE)** can give sufficient anatomical data about the site and size of the defect.

Any abnormal pathways predisposing to atrial flutter/fibrillation should be considered for **RFA** radiofrequency ablation which can be curative.

**NB**: Atrial fibrillation is associated more with atrial septal defects

**NB**: In the **presence** of **Eisenmenger's syndrome**, the **maternal mortality** is approximately **40%** and **pregnancy is contraindicated**, with **older** maternal age increasing the risk of **pulmonary hypertension** and **Eisenmenger's**.

In the **absence** of any structural heart disease or Eisenmenger's, the pregnant woman with ASD has **no** significant increase in risk compared to the general population.

## Lutembacher's syndrome (= MS+ ASD± AF):

- This was first described in 1916 by Lutembacher, and is a syndrome characterised by both mitral stenosis and atrial septal defect (ASO).
- Both conditions may be congenital and occur concurrently, or the mitral stenosis may occur as a result of rheumatic fever or other cause. Incidence of Lutembacher's syndrome is higher in women due to the higher incidence of congenital ASO.
- Cardiac signs are mixed due to the two concurrent lesions.
- Presentation is typically in later life, with fatigue or atrial fibrillation. Ideally, surgery should be performed as early as possible due to the risks of Eisenmenger's syndrome in untreated patients.

**Atrial Septal Defects make up 30%of congenital heart disease** detected in the adult population.

- The Female-male ratio is 2:1 and 75%of them are ostia secunda.
- They commonly present during pregnancy with either breathlessness or palpitations.
- There usually is no audible murmur with ASDs.
- The combination of right bundle branch block (RBBB) and right axis deviation on theelectrocardiogram (ECG) makes an ostium secundum ASD more likely.
- These patients should have urgent echocardiographic assessment to assess the state of the right heart and be followed up *very* closely as the prognosis is *very* poor if they develop Eisenmerger's syndrome; early surgical intervention after the birth of the child is a consideration.

**Pregnant female + Palpitation + incomplete RBBB + fixed S2 splitting = Ostium secundum ASD and needs Urgent Echo and urgent surgical intervention after delivery.COMMON MCQ**

## Patent Foramen Ovale (PFO)

Patent foramen ovale (PFO) is present in around **20%** of the population.

It may allow embolus (e.g. from DVT) to pass from right side of the heart to the left side leading to a stroke - **'a paradoxical embolus'.**

Whilst atrial septal defects may allow emboli to pass from the right side of the heart to the left side**, but the most common cause is a patent foramen ovale**.
There also appears to be an association between **migraine and PFO**. Some studies have reported improvement in migraine symptoms following closure of the PFO.

**Transoesophageal echocardiography (TOE)** is the investigation of choice to investigate for a PFO, although transthoracic echocardiography with bubble contrast may be an alternative.

## Paradoxical embolisation

For a right-sided thrombus (e.g. DVT) to cause a left-sided embolism (e.g. stroke) it must obviously pass from the right-to-left side of the heart.
**The following cardiac lesions may cause such events:**

- **Patent foramen ovale (PFO)**: present in **around 20% of the population.**
- **Atrial septal defect (ASD):** much less common cause.

**Transoesophageal echocardiography (TEE)** provides superior views of the atrial septum and therefore is preferred to transthoracic echocardiography for detecting patent foramen ovale.

| |
|---|
| **NB**: EX. a 24-year-old female develops transient slurred speech following a flight from Australia to the United Kingdom. Both a CT head and ECG are normal. Which one of the following tests is most likely to reveal the underlying cause? |
| A: Paradoxical embolus >>> PFO most common cause >>> do TEE. |

# Eisenmenger's syndrome

Eisenmenger's syndrome describes the reversal of a left-to-right shunt in a congenital heart defect due to **pulmonary hypertension.**

This occurs when an uncorrected left-to-right leads to **remodelling** of the pulmonary microvasculature, eventually causing obstruction to pulmonary blood and pulmonary hypertension.

The original murmur may **disappear** once Eisenmenger's syndrome develops.

## Associated with:

- Ventricular septal defect.
- Atrial septal defect.
- Patent ductus arteriosus.

## Features:

- **Original murmur may disappear**
- **Cyanosis**
- **Clubbing**
- Right ventricular failure
- Haemoptysis, embolism

## Management:

- Heart-lung transplantation is required

**NB:** Although patients with tetralogy of Fallot have, by definition, a ventricular septal defect they do not go on to develop Eisenmenger's syndrome.
**NB:** The **reversed patent ductus arteriosus (PDA)** >>> There is a **right-left shunt** from the pulmonary artery to the aorta just **distal** to the **left subclavian artery** >>> Pt 25 yrs. with **cyanosis of the lower limbs and clubbing of the toes** but **not the fingers.**

# Tetralogy of Fallot (TOF)

TOF is the most common cause of cyanotic congenital heart disease.
It typically presents at around 1-2 months, although may not be picked up until the baby is 6 months old.

However, at birth the transposition of the great arteries (TGA) is the more common lesion as patients with TOF generally present at around 1-2 months

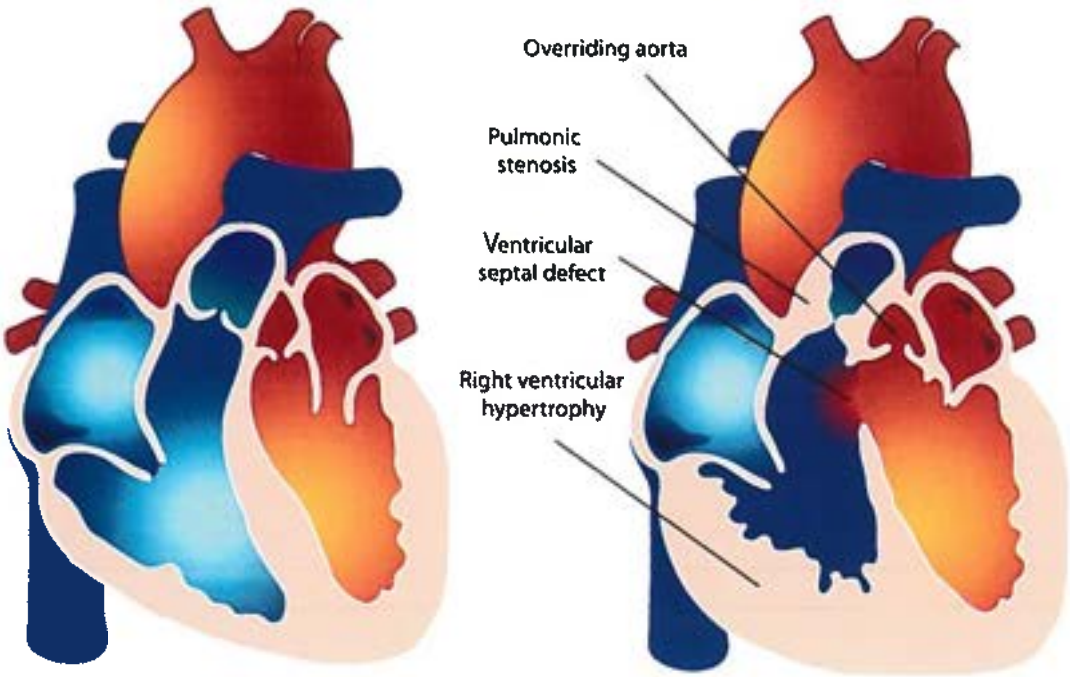
TOF is a result of anterior mal-alignment of the **aortico-pulmonary septum**.

## The four characteristic features are:

1) **Ventricular septal defect (VSD)**
2) **Right ventricular hypertrophy**
3) **Right ventricular outflow tract obstruction, pulmonary stenosis**
4) **Overriding aorta**

Normal heart

**Tetralogy of Fallot**




The **severity of the right ventricular outflow tract obstruction** determines the degree of cyanosis and clinical severity.

### Other features:

- **Cyanosis**
- Causes a **right-to-left shunt**
- **Ejection systolic murmur** due to **pulmonary stenosis**

**N.B:** the **VSD doesn't** usually cause a murmur.

- A right-sided aortic arch is seen in 25% of patients
- CXR shows a **'boot-shaped' heart.**
- ECG shows right ventricular hypertrophy.

### Management:

- **Surgical** repair is often undertaken **in two parts.**
- **A Blalock shunt** (anastomosis of subclavian artery to pulmonary artery) it leads to a weak left radial pulse.
- Cyanotic episodes may be helped by **beta-blockers** to reduce infundibular spasm.

**NB: ASD, VSD and PDA >>> Lt to RT Shunt,**
**But, TOF >>>> RT to Lt Shunt.**

## Coarctation of the aorta

Coarctation of the aorta describes a congenital narrowing of the **descending aorta.** The most common type of coarctation of the aorta seen in adults is the **post-ductal** variety, i.e. the aortic narrowing is **distal** to the ductus arteriosus.

This means that the **upper limb** BP is **greater** than that in the lower limbs as the narrowing occurs after the left subclavian artery branches from the aorta.

**Overview:** More common in **males** (despite association with Turner's syndrome)

### Features:

- Infancy: heart failure
- Adult: hypertension
- **Radio-femoral delay**
- Mid **systolic** murmur, **maximal over back (thoracic spines)**
- Apical click from the aortic valve
- **Notching of the inferior border of the ribs** (due to collateral vessels) is not seen in young children **(scalloping of the posterior ribs on CXR).**

### Associations: (4)

1) **Turner's** syndrome.
2) **Bicuspid aortic valve.**
3) **Berry aneurysms.**
4) **Neurofibromatosis.**

## Epstein's anomaly

It is a **rare** condition probably accounting for around **0.5%** of cases of congenital heart disease.

Epstein's anomaly is a congenital heart defect characterised by **low insertion** of **the tricuspid valve** (displacement of the tricuspid valve towards the apex) resulting in a large atrium and small ventricle.

It is sometimes referred to as **'arterialisation' of the right ventricle** and **hypoplastic RV** and an associated defect such as **ASD**.

### Associations:

- patent foramen ovale (PFO) or atrial septal defect (ASD) is seen in at least 80% of patients, resulting in a shunt between the right and left atria
- Wolff-Parkinson White syndrome

### Clinical features

- cyanosis
- prominent 'a' wave in the distended jugular venous pulse,
- hepatomegaly
- tricuspid regurgitation
  - **pansystolic murmur, worse on inspiration**
- right bundle branch block → widely split S1 and S2

## Transposition of the great arteries

Transposition of the great arteries (TGA) is a form of cyanotic congenital heart disease. It is caused by the **failure of the aorticopulmonary septum to spiral during septation**.

Children of diabetic mothers are at an increased risk of TGA.

### Basic anatomical changes

- aorta leaves the right ventricle
- pulmonary trunk leaves the left ventricle

### Clinical features

- cyanosis
- tachypnoea
- loud single S2
- prominent right ventricular impulse
- 'egg-on-side' appearance on chest x-ray

### Management

- maintenance of the ductus arteriosus with prostaglandins
- surgical correction is the definite treatment.

# Syncope

## Syncope

defined as a **transient loss of consciousness** due to **global cerebral hypoperfusion** with **rapid onset, short duration** and **spontaneous complete recovery.** Note how this definition excludes other causes of collapse such as epilepsy.
The European Society of Cardiology published guidelines in 2009 on the investigation and management of syncope. They suggested the following three classification:

### 1) Reflex syncope (neurally mediated):

- **Vasovagal:** triggered by emotion, pain or stress. Often referred to as 'fainting'
- **Situational**: cough, micturition, gastrointestinal
- **Carotid** sinus hypersensitivity (CSH)

This patient has carotid sinus hypersensitivity (CSH), demonstrating an exaggerated response to carotid Sinus stimulation. The diagnosis is only made after ischaemic heart disease or rhythm disturbance have been reasonably excluded, as in this case. CSH may be predominantly cardioinhibitory (resulting in bradycardia), vasodilatory (resulting in hypotension), or a mixture of the two. Cardioinhibitory CSH is usually managed with insertion of a dual-chamber pacemaker, and vasodilatory CSH is managed with support stockings, fludrocortisone and midodrine (available on a named-patient basis in the UK)

### 2) Orthostatic syncope:

- **Primary autonomic failure**: Parkinson's disease, Lewy body dementia
- **Secondary autonomic failure:** e.g., Diabetic neuropathy, amyloidosis, uraemia
- **Drug-induced:** diuretics, alcohol, vasodilators
- **Volume depletion:** haemorrhage, diarrhoea

### 3) Cardiac syncope:

- **Arrhythmias:** bradycardias (sinus node dysfunction, AV conduction disorders) or tachycardias (supraventricular, ventricular).
- **Structural:** valvular, myocardial infarction, hypertrophic obstructive cardiomyopathy.
- **Others:** pulmonary embolism.

**Reflex syncope is the most common cause in all age groups** although orthostatic and cardiac causes become progressively more common in older patients.

## Evaluation:

- Cardiovascular examination
- Postural blood pressure readings: a symptomatic fall in systolic BP > 20 mmHg or diastolic BP > 10 mmHg or decrease in systolic BP < 90 mmHg is considered diagnostic.
- ECG, 24 hour ECG
- Carotid sinus massage
- **Tilt table test**

**N.B**: The normal pulmonary circulation is characterised by >> **low pressures**, **low flow rates**, **high compliance** vessels than that of the systemic circulation

# Miscellaneous

## Exercise tolerance tests

Exercise tolerance tests (ETT, also exercise ECG) are used for a variety of

### indications:

- assessing patients with suspected angina - however the 2010 NICE Chest pain of recent onset guidelines do not support the use of ETTs for all patients
- risk stratifying patients following a myocardial infarction
- assessing exercise tolerance
- risk stratifying patients with hypertrophic cardiomyopathy

ETT has a sensitivity of around 80% and a specificity of 70% for ischaemic heart disease.

### Heart rate:

- maximum predicted heart rate = 220 - patient's age
- the target heart rate is at least 85% of maximum predicted to allow reasonable interpretation of a test as low-risk or negative

### Contraindications

- myocardial infarction less than 7 days ago
- unstable angina
- uncontrolled hypertension (systolic BP > 180 mmHg) or hypotension (systolic BP < 90 mmHg)
- aortic stenosis
- left bundle branch block: this would make the ECG very difficult to interpret

### Stop if:

- exhaustion / patient request
- 'severe', 'limiting' chest pain
- > 3mm ST depression
- > 2mm ST elevation.Stop if rapid ST elevation and pain
- systolic blood pressure > 230 mmHg
- systolic blood pressure falling > 20 mmHg
- attainment of maximum predicted heart rate
- heart rate falling > 20% of starting rate
- arrhythmia develops

# Adult advanced life support

The following is based on the 2015 Resus Council guidelines. Please see the link for more details, below is only a very brief summary of key points.

It should be remembered that the algorithm divides patients into those with:

- 'shockable' rhythms: ventricular fibrillation/pulseless ventricular tachycardia (VF/pulseless VT)
- 'non-shockable' rhythms: asystole/pulseless-electrical activity (asystole/PEA)

## Major points include:

### chest compressions

- the ratio of chest compressions to ventilation is 30:2
- chest compressions are now continued while a defibrillator is charged

### defibrillation

- **a single shock for VF/pulseless VT** followed by 2 minutes of CPR
- if the cardiac arrested is witnessed in a monitored patient (e.g. in a coronary care unit) then the 2015 guidelines recommend 'up to three quick successive (stacked) shocks', rather than 1 shock followed by CPR

### drug delivery

- IV access should be attempted and is first-line
- if IV access cannot be achieved then drugs should be given via the intraosseous route (IO)
- delivery of drugs via a tracheal tube is no longer recommended

### adrenaline

- **adrenaline 1 mg as soon as possible for non-shockable rhythms**
- during a VF/VT cardiac arrest, **adrenaline 1 mg** is given once chest compressions have restarted after the third shock
- repeat adrenaline 1mg every 3-5 minutes whilst ALS continues

### amiodarone

- amiodarone 300 mg should be given to patients who are in VF/pulseless VT after 3 shocks have been administered.
- a further dose of amiodarone 150 mg should be given to patients who are in VF/pulseless VT after 5 shocks have been administered
- lidocaine used as an alternative if amiodarone is not available or a local decision has been made to use lidocaine instead

### thrombolytic drugs

- should be considered if a pulmonary embolus is suspected
- if given, CPR should be continued for an extended period of 60-90 minutes

## Other points

- atropine is no longer recommended for routine use in asystole or pulseless electrical activity (PEA)
- following successful resuscitation oxygen should be titrated to achieve saturations of 94-98%. This is to address the potential harm caused by hyperoxaemia.

Reversible causes of cardiac arrest:

| The 'Hs' | The 'Ts' |
|---|---|
| • Hypoxia<br>• Hypovolaemia<br>• Hyperkalaemia, hypokalaemia, hypoglycaemia, hypocalcaemia, acidaemia and other metabolic disorders<br>• Hypothermia | • Thrombosis (coronary or pulmonary)<br>• Tension pneumothorax<br>• Tamponade – cardiac<br>• Toxins |

# DVLA important notes

Notifiable conditions are anything that could affect the ability to drive safely. They can include:

- **diabetes or taking insulin**
- **syncope (fainting)**
- heart conditions (including **atrial fibrillation** and **pacemakers)**
- **sleep apnea**
- **epilepsy**
- **strokes**
- **glaucoma**

## DVLA: cardiovascular disorders

The guidelines below relate to car/motorcycle use unless specifically stated. For obvious reasons, the rules relating to drivers of heavy goods vehicles tend to be much stricter

### Specific rules

- **hypertension**
  - can drive unless treatment causes unacceptable side effects, no need to notify DVLA
  - if Group 2 Entitlement the disqualifies from driving if resting BP consistently 180 mmHg systolic or more and/or 100 mm Hg diastolic or more
- **angioplasty (elective)** - 1 week off driving

- **CABG** - 4 weeks off driving
- **acute coronary syndrome**- 4 weeks off driving
  - 1 week if successfully treated by angioplasty
- angina - driving must cease if symptoms occur at rest/at the wheel
- **pacemaker insertion** - 1 week off driving
- **implantable cardioverter-defibrillator** (ICD)
  - if implanted for sustained ventricular arrhythmia: cease driving for 6 months
  - if implanted prophylactically then cease driving for 1 month. Having an **ICD results in a permanent bar for Group 2 drivers**
- successful catheter ablation for an arrhythmia- 2 days off driving
- aortic aneurysm of 6cm or more - notify DVLA. Licensing will be permitted subject to annual review.
  - an aortic diameter of 6.5 cm or more disqualifies patients from driving
- **heart transplant:** do not drive for 6 weeks, no need to notify DVLA

EXample: Pt with post MI and had received thrombolytic therapy >>> he has to stop driving, inform the DVLA, and return for exercise ECG test in 6 weeks while off all anti-angina medications as β blocker (not ASA or Plavix) for 48 hours before. There should be no residual chest pain or significant ECG changes.

## Atrial myxoma

### Overview:

- 75% occur in **left atrium.**
- More common in **females.**

### Features:

- It is **the most common primary heart tumour.**
- It produces symptoms either through distant embolization or mechanical interference with cardiac function.
- One third present with emboli, a third with systemic inflammation (ESR elevated in 1/3) and a third are asymptomatic when detected.
- Systemic: **exertional dyspnoea in 75%,** fatigue, **weight loss, fever, clubbing,** dizziness, **syncope (dt obstruction of mitral valve),** and **sudden cardiac death in 15%.**
- **Emboli.**
- **Atrial fibrillation.**
- **Loud S1** due to delay in mitral valve closure due to prolapse of the tumour into the mitral valve orifice.

- **Mid-diastolic murmur**, 'tumour **plop**' (↑ **with sitting forward).**
- Echo: pedunculated heterogeneous mass **typically attached to the fossa ovalis region** of the **interatrial septum.**
- **CXR: intra-cardiac calcification**

**Carney's complex is a familial multiple neoplasia and lentiginose syndrome, associated with**

- **Primary adrenal hypercortisolism**
- Lentigines and naevi of the skin
- Various tumours including myxoma.

Although rare (2 per 100 000 with a female to male ratio of 2:1) the diagnosis of atrial myxoma should be entertained in a person who presents with finger clubbing normocytic anaemia a positional murmur and intracardiac calcification in the chest X-ray The All history of fainting spells suggests transient left ventricular inflow obstruction. The patient should undergo urgent echocardiography and be referred for Surgery if the diagnosis of myxoma is confirmed, as complete removal is curative

## Cardiac transplantation

By **5** years following cardiac transplantation >>> nearly **all** patients have some degree of **Coronary arteriopathy (small coronary vascular narrowing)** >>> fatigue with exercise, pedal oedema, Bibasilar crackles and orthopnoea.

**Bradycardia** and **syncope** in patient with **cardiac transplant** >>> the pharmacotherapy of bradycardias is different for this group of patients. This is because the transplanted heart is **denervated.**

Therefore there is **no place for atropine**, **even at higher doses**, hence repeated doses of atropine at 500 mcg per dose or at 1 mg per dose are incorrect, The Resuscitation Council (UK) guidelines suggest using **theophylline IVI** as a slow intravenous infusion (100-200 mg).

**NB**: Becker muscular dystrophy is an X-linked genetic disorder resulting from a mutation in the dystrophin gene. The clinical picture is similar to that of Duchenne's muscular dystrophy but it is much milder. Patients usually present between the ages of 5 and 15 years, though presentation may not be until the fourth or fifth decade. Patients may present with heart failure secondary to dilated cardiomyopathy instead of the classic proximal muscle weakness. Inheritance is X-linked recessive.

**NB: Tocolysis-associated pulmonary oedema:**
Tocolytics are medications administered for the suppression of premature contractions. Acute pulmonary oedema can occur with administration of β2 agonists for tocolysis in up to 5-15% of cases. It usually occurs after 24 h of administration of these agents The chest X-ray reveals pulmonary infiltrates and normal heart size. Concomitant use of corticosteroids that are often administered for lung maturation have also been implicated as risk factor for development of tocolysis-associated pulmonary oedema. Treatment involves stopping the tocolytics Oxygen and careful volume control. Peripartum cardiomyopathy and myocarditis cause Systolic dysfunction and will be expected to show cardiomegaly on chest X-ray. Pulmonary embolism is unlikely to cause bilateral chest infiltrates. As the Patient's examination was normal prior to this event mitral stenosis is less likely

**EX**: pregnant female admitted in hospital with premature labour and received tocolysis IV then developed acute dyspnoea >>>> **Tocolysis-associated pulmonary oedema**

## Kawasaki disease

Kawasaki disease is a type of vasculitis which is predominately seen in children. Whilst Kawasaki disease is uncommon it is important to recognise as it may cause potentially serious complications, including coronary artery aneurysms.

### Features:

- high-grade fever which lasts for > 5 days. Fever is characteristically resistant to antipyretics
- conjunctival injection
- bright red, cracked lips
- strawberry tongue
- cervical lymphadenopathy
- red palms of the hands and the soles of the feet which later peel

**Kawasaki disease is a clinical diagnosis as there is** no specific diagnostic test.

### Management:

- high-dose aspirin
  - Kawasaki disease is one of the few indications for the use of aspirin in children. Due to the risk of Reye's syndrome aspirin is normally contraindicated in children
- **intravenous immunoglobulin**
- echocardiogram (rather than angiography) is used as the initial screening test for coronary artery aneurysms

### Complications: coronary artery aneurysm

# Down syndrome (Triosmy 21):

## Features:

### Clinical features:

- Face: upslanting palpebral fissures, epicanthic folds, Brushfield spots in iris, protruding tongue, small ears, round/flat face
- Flat occiput
- Single palmar crease, pronounced 'sandal gap' between big and first toe
- Hypotonia
- **Congenital heart defects (40-50%)**
- **GIT malformations** (6%):
  - **Duodenal atresia** ('double bubble' sign.)
  - **Hirschsprung's disease**

**complications:** **Cardiac** (Multiple cardiac problems may be present):

- **Endocardial cushion defect** (c. **40%,** also known as **complete atrioventricular septal canal defects)**
- VSD (c. 30%)
- Secundum ASD (c. 10%)
- Tetralogy of Fallot (c. 5%)
- Isolated PDA (c. 5%)

### Later complications:

- Fertility problems:
  - **Males** are almost always **infertile** due to impaired spermatogenesis.
  - **Females** are usually **subfertile**, and have an increased incidence of problems with pregnancy and labour.
- Learning difficulties
- **Short stature**
- Repeated respiratory infections (+hearing impairment from glue ear)
- Acute lymphoblastic leukaemia (ALL)
- **Hypothyroidism**
- **Alzheimer's**
- **Atlantoaxial instability**

Down's syndrome >>>> **Endocardial cushion defects (complete atrioventricular septal canal defects)** account for about **40%** of congenital heart disease.

# Turner's syndrome

Turner's syndrome is a chromosomal disorder affecting around 1 in 2,500 females.

It is caused by either the presence of only one sex chromosome (X) or a deletion of the short arm of one of the X chromosomes.

It is denoted by **lymphocyte karyotyping** as **45, XO** or **45, X**

## Features:

- **Short stature**
- Shield chest, **widely spaced nipples**
- **Webbed neck.**
- **Bicuspid aortic valve (15%)** and **Coarctation of the aorta (5-10%)**
- **HTN:** is quite common (10%) and is typically idiopathic (essential).
- **Primary amenorrhoea.**
- Cystic hygroma (often diagnosed prenatally)
- **High-arched palate**
- Short fourth metacarpal
- Cubitus valgus.
- Osteoporosis
- Multiple pigmented naevi
- **Lymphoedema** in neonates (especially feet)
- **Congenital malformations of the renal tracts.**
- Increased incidence of **autoimmune** disease (especially **autoimmune Hashimoto's thyroiditis**) and **Crohn's** disease

**Hypothyroidism** is common occurring in up to **24%** of pts with Turner's S.

Turner's syndrome >> most common cardiac defect is **bicuspid aortic valve**

Turner's syndrome >>>Surveillance **echocardiography** and **renal US** are recommended.

**EX. Young female** with **1ry amenorrhea** + **1 ry HTN** >>>>> think of: Turner syndrome or congenital adrenal hyperplasia.

# Marfan's syndrome

Marfan's syndrome is an **autosomal dominant** connective tissue disorder, so usually his parents are also very tall or sometimes mutation and he is the tallest among his family

It is caused by a defect in the **fibrillin-1 gene** on chromosome 15 and affects around **1 in 3,000** people.

**Unfortunately** DNA testing for fibrillin gene mutations, whilst helpful, it cannot exclude the diagnosis of Marfan's because of a number of mutations exist, at least **130 mutations**.

Hence diagnosis is based on the major and minor Marfan's **features**.

## Features:

- Tall stature with **arm span to height ratio > 1.05** and
- **Upper to lower body ratio** is **decreased** (head to symphysis pubis: symphysis pubis to toes).
- High-arched palate
- Arachnodactyly
- **Pectus excavatum**
- Pes planus
- **Scoliosis** of > 20 degrees >>> Low back pain.
- **Dural ectasia** (ballooning of the dural sac at the lumbosacral level): Dural ectasia affects around **60%** of patients with Marfan's syndrome. It may cause **lower back pain** associated with **neurological problems** such as **bladder** and **bowel** dysfunction like incontinence.
- **Heart:**
  - **Dilatation of the aortic sinuses (seen in 90%)** which may lead to aortic **regurgitation**, aortic **aneurysm**, aortic **dissection**, and
  - **Mitral valve prolapse (MVP) (75%)**: systolic murmur at mitral area.
- **Lungs: repeated pneumothoraxes**
- **Eyes: Upwards(downword in homocystinuria)** lens dislocation (supertemporal ectopia lentils), **blue sclera, retinal detachment** and **myopia.**

The life expectancy of patients used to be around 40-50 years.
With the advent of **regular echocardiography monitoring** and **beta-blocker/ACE-inhibitor** therapy this has improved significantly over recent years.

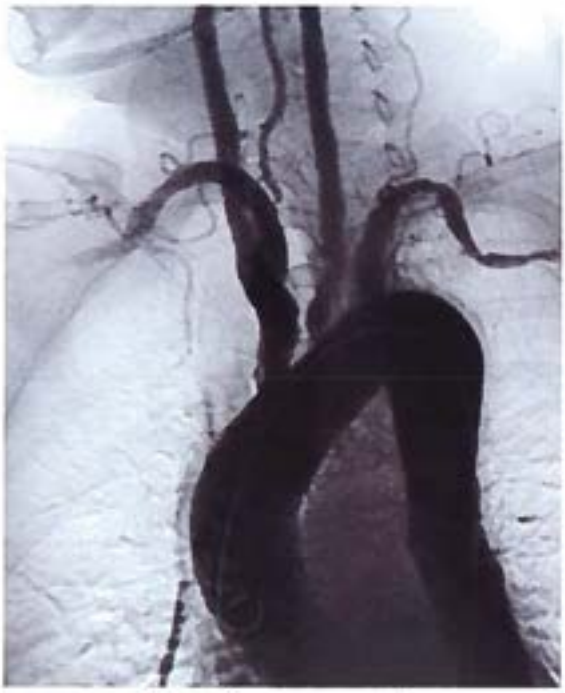
Aortic dissection and other cardiovascular problems remain the leading cause of death however.

# Takayasu's arteritis

Takayasu's arteritis is a large vessel vasculitis. It typically causes occlusion of the aorta and questions commonly refer to an absent limb pulse. It is more common in younger females (e.g. 10-40 years) and Asian people.

## Features:

- systemic features of a vasculitis e.g. malaise, headache
- unequal blood pressure in the upper limbs
- carotid bruit and tenderness
- absent or weak peripheral pulses
- upper and lower limb claudication on exertion
- aortic regurgitation (around 20%)



Angiography showing multiple stenoses in the branches of the aorta secondary to Takayasu's arteritis

## Associations:

- renal artery stenosis

## Management:

- steroids

## Fat embolism syndrome

Fat embolism syndrome is a **clinical** diagnosis secondary to the presence of fat globules in the lung parenchyma and circulation that are typically released following **long bone fractures**.

It requires **high index of suspicion** and usually presents **12-72 hours after initial injury**.

### There is a classic triad of:

- **Respiratory** changes - Dyspnoea, tachypnoea and hypoxaemia are early findings. These may progress to respiratory failure and ARDS requiring mechanical ventilation.
- **Neurological** features - Cerebral emboli produce neurological signs in up to **86%** cases. They often occur after onset of respiratory symptoms, with a wide spectrum ranging from **mild confusion and drowsiness** to **seizures.** Usually there is an acute confusional state with or without focal signs. Most neurological deficits are transient and reversible.
- **Petechial** rash - This is the final component of the triad to develop and occurs in **60%** of cases. Rash is seen in the conjunctiva, mucous membranes, skin folds of upper body particularly neck and axilla, appearing within the first 36 hours.

### Patients may also develop:

- Pyrexia
- Tachycardia
- ECG changes (ST segment depression and right heart strain)
- Fluffy retinal exudates
- Coagulopathy, and
- Renal changes (oliguria, lipiduria, proteinuria or haematuria).

## Cholesterol embolization syndrome

### Overview:

- It is most commonly seen in patients with **existing arterial disease** who have undergone arterial **manipulation**.
- Seen more commonly in **arteriopathy**, abdominal aortic aneurysms.
- Pre-existing renal impairment, DM and hypovolaemia at time of procedure are all associated with **increased risk**.

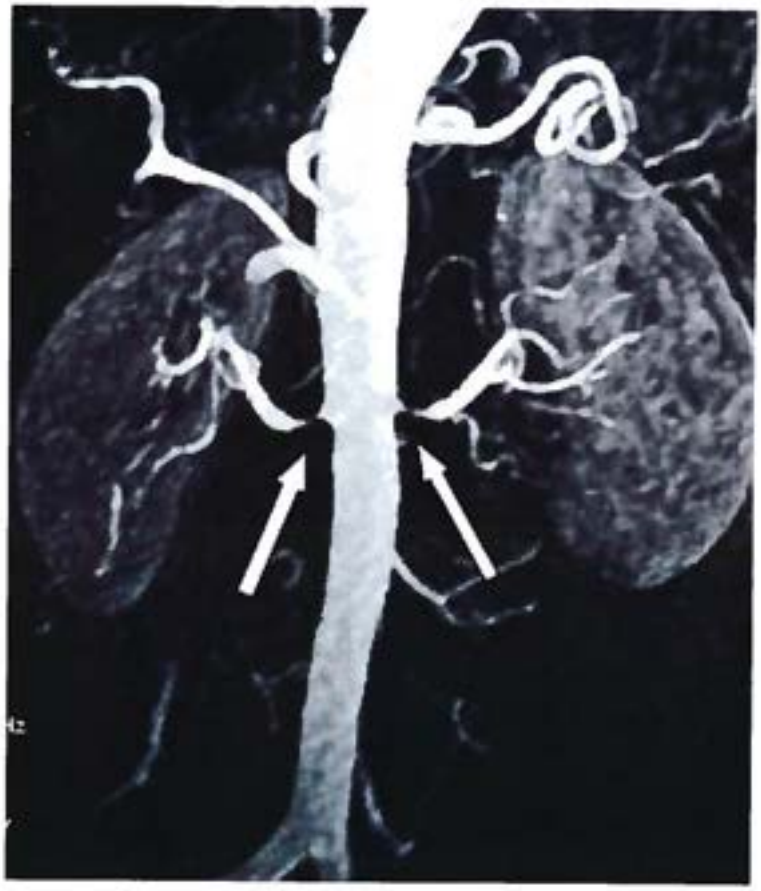
- Cholesterol emboli may break off causing renal disease.
- Ulceration of an **atheromatous plaque** of the **abdominal aorta** especially in **elderly** patient can cause embolus in his femoral artery leading to absent leg pulse.
- Data are largely based on post mortem examinations.
- Some studies suggest that as many as **25-30%** of patients undergoing angiography will have atherosclerotic emboli.

**Features:**

- **Eosinophilia** (present in **70%** of cases)
- **Purpura**
- **Livedo reticularis**
- **Renal failure**
- **Acute abdomen** due to bowel ischaemia.

**Treatment:** Unfortunately, there is **no specific treatment** shown to be of benefit.

**EX**: A 62-year-old male is admitted with an inferior MI and receives thrombolysis. His ECG shows good ST segment resolution. The following day he develops some **pain** in the **legs** and a **dusky discolouration** of the lower limbs. On closer examination there is a **diffuse petechial rash** over the lower legs, particularly the **feet**, with **raised TLC - marked eosinophilia** , raised **ESR**, raised **IgE** and low complement. But **all peripheral pulses are palpable** >> **Cholesterol embolisation syndrome.** Peripheral pulses are intact because cholesterol emboli are **microcrystals** which are too small to occlude medium sized arteries.



Angiogram revealing bilateral renal artery stenosis (arrows), one of the more common causes of secondary hypertension, most often a result of atherosclerotic disease in older patients. (Reproduced with permission from Fuster V, Walsh R, Harrington RA: Hurst the Heart, 13th ed. New York, NY: McGraw-Hill Education; 2011.)

Flash pulmonary oedema, U&Es worse on ACE inhibitor, asymmetrical kidneys → **renal artery stenosis (RAS)** - do **MRA** angiography.

**Flash pulmonary oedema** in someone with a history of **hypertension**, especially those suspected of being arteriopaths such as **smokers**, should raise the possibility of **renal artery stenosis.**

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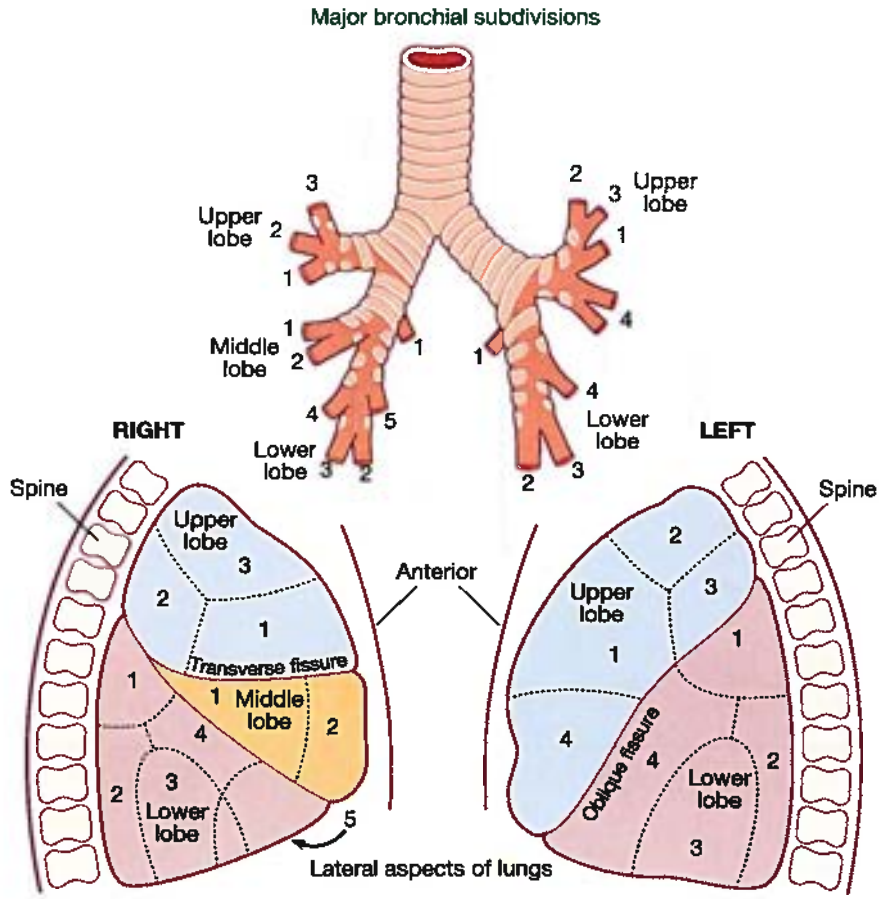
# Anatomy of the lung




The major bronchial divisions and the fissures, lobes and segments of the lungs. The angle of the oblique fissure means that the left upper lobe is largely anterior to the lower lobe. On the right, the transverse fissure separates the upper from the anteriorly placed middle lobe, which is matched by the lingular segment on the left side. The site of a lobe determines whether physical signs are mainly anterior or posterior. Each lobe is composed of two or more bronchopulmonary segments that are supplied by the main branches of each lobar bronchus.

**Bronchopulmonary segments:**

**Right Upper lobe**: **(1)** Anterior, **(2)** Posterior, **(3)** Apical.

**Middle lobe:** **(1)** Lateral, **(2)** Medial.

**Lower lobe:** **(1)** Apical, **(2)** Posterior basal, **(3)** Lateral basal, **(4)** Anterior basal, **(5)** Medial basal.

**Left Upper lobe:** **(1)** Anterior, **(2)** Apical, **(3)** Posterior, **(4)** Lingular.

**Lower lobe:** **(1)** Apical, **(2)** Posterior basal, **(3)** Lateral basal, **(4)** Anterior

# Azygous lobe

An azygous lobe is seen in about **0.5%** of routine CXR

It is a **normal variant**. It has **little** clinical significance.

It is seen as a **'reverse comma sign'** behind the **medial end** of the **right clavicle** on the **upper zone** of the **right lung**.

It appears separated from the rest of the upper lobe by a deep groove (which contains the azygous vein).
In develops in utero when the apical bronchus grows medial to the arch of the azygous vein instead of lateral.

# Respiratory physiology

## Lung volumes

**Tidal volume (TV):**

- Volume inspired or expired with each breath at rest
- 500ml in males, 350ml in females

**Inspiratory reserve volume (IRV) = 2-3 L:**

- Maximum volume of air that can be **inspired** at the end of a normal tidal inspiration
- Inspiratory capacity = TV + IRV

**Expiratory reserve volume (ERV) = 750ml:**

- Maximum volume of air that can be **expired** at the end of a normal tidal expiration

**Residual volume (RV) = 1.2L:**

- Volume of air remaining after maximal expiration
- Increases with age
- RV = FRC - ERV

**Vital capacity (VC) = 5L:**

- **Maximum volume of air that can be expired after a maximal inspiration**
- **4,500** ml in **males** and **3,500** ml in **females**
- Decreases with age
- VC = inspiratory capacity + ERV

**Total lung capacity (TLC):** is the sum of the vital capacity + residual volume

**Physiological dead space ($V_D$):**

- $V_D$ = tidal volume * ($PaCO_2$ - $PeCO_2$) / $PaCO_2$
- where $PeCO_2$ = expired air $CO_2$

# Respiratory physiology: Control of respiration

- **Central** regulatory centres at pons and medulla
- Central and peripheral **chemoreceptors**
- **Pulmonary** receptors

## 1) Central regulatory centres at pons and medulla:

- Apneustic centre (lower pons).
- Pneumotaxic centre (upper pons).
- Medullary respiratory centre.

## 2) Central and peripheral chemoreceptors:

- Central: **raised [H+]** in **ECF >>> stimulates respiration.**
- Peripheral: **carotid + aortic bodies**, respond to raised pCO2 & [H+], **lesser extent low pO2.**

## 3) Pulmonary receptors:

- **Stretch** receptors, lung **distension** causes **slowing** of respiratory rate (**Hering-Bruer reflex**).
- Irritant receptor, leading to bronchoconstriction.
- Juxtacapillary receptors, stimulated by stretching of the microvasculature.

## Chloride shift:

- $CO_2$ diffuses into RBCs
- $CO_2 + H_2O$ ---- carbonic anhydrase ⟶ $HCO_3^- + H^+$
- $H^+$ combines with Hb
- $HCO_3^-$ diffuses out of cell,- $Cl^-$ replaces it

## Bohr Effect:

- Increasing **acidity** (or **PCO2**) means **O2 binds less well to Hb**.

## Haldane effect:

- Increase **PO2** means **CO2 binds less well to Hb**.

# Respiratory physiology: hypoxia

A fall in the partial pressure of oxygen in the blood leads to **vasoconstriction** of the **pulmonary** arteries.

This **allows blood to be diverted to better aerated areas** of the lung and improves the efficiency of gaseous exchange.

The **pulmonary arteries** (NOT the skin arteries) is the **first** type of blood vessel to **vasoconstrict** in the presence of **hypoxia.**

## Respiratory physiology: lung compliance (C=V/P)

Lung compliance is defined as change in lung **volume** per unit change in airway **pressure**.

| Causes of increased compliance | Causes of decreased compliance |
|---|---|
| • **Age**<br>• **Emphysema** - this is due to loss alveolar walls and associated elastic tissue | • Pulmonary **oedema**<br>• Pulmonary **fibrosis**<br>• **Pneumonectomy**<br>• **Kyphosis** |

The **pathophysiological** changes which is most responsible for **emphysema** is **Destruction of alveolar walls secondary to proteinases**.

Proteinases such as **elastase** cause **irreversible** damage to the supporting connective tissue of the alveolar septa.
Smoking accelerates this process.
ar septa. Smoking accelerates this process.

## Respiratory acidosis

### Respiratory acidosis: causes:

Respiratory acidosis may be caused by a number of conditions:

- **COPD**
- decompensation in other respiratory conditions e.g. **life-threatening asthma** / pulmonary oedema
- **neuromuscular disease**
- **obesity hypoventilation syndrome**
- sedative drugs: **benzodiazepines, opiate overdose**

## Respiratory alkalosis

### Respiratory alkalosis: causes:

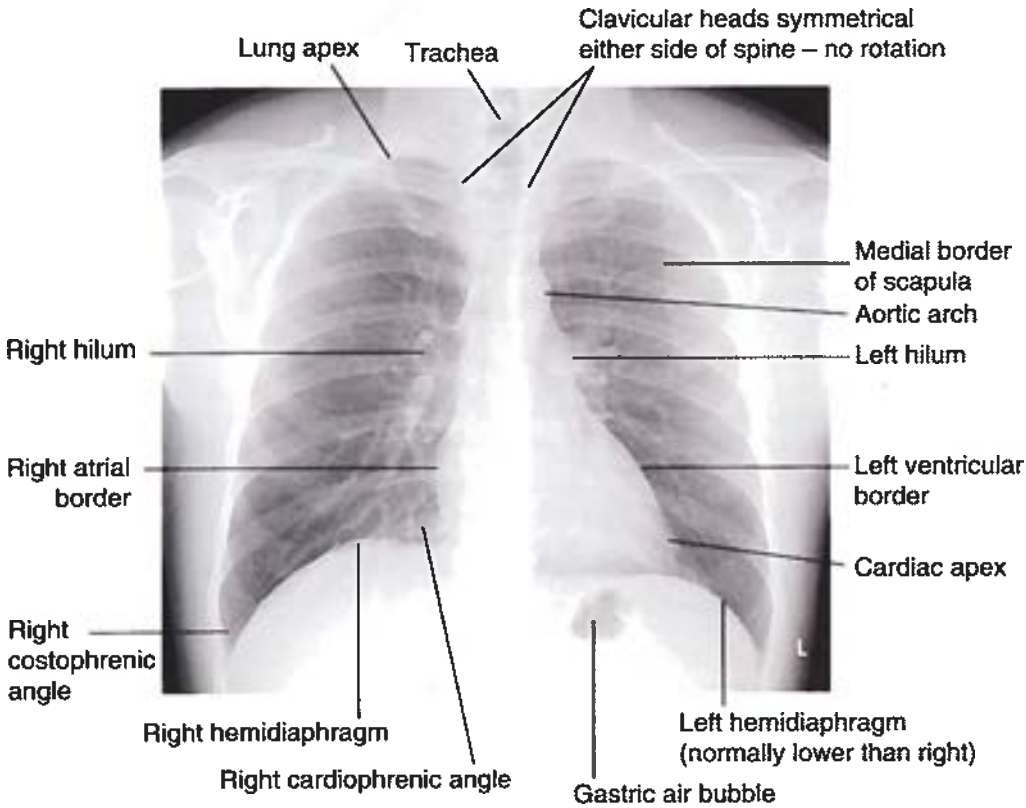
- **Acute severe asthma**
- **Pulmonary embolism**
- **Anxiety leading to hyperventilation**
- **Salicylate** poisoning*
- **CNS** disorders: stroke, subarachnoid haemorrhage, encephalitis
- **High altitude**
- **Pregnancy**

**Salicylate** overdose leads to a **mixed** **respiratory alkalosis** and **metabolic acidosis:**

- **Early** stimulation of the respiratory centre leads to a respiratory alkalosis.
- Whilst **later** the direct acid effects of salicylates (combined with acute renal failure) may lead to an acidosis.

## How to interpret a chest X-ray

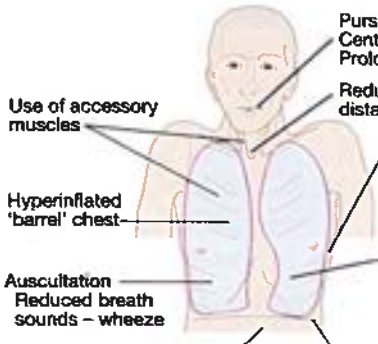
| How to interpret a chest X-ray | |
|---|---|
| **Name, date, orientation** | Films are posteroanterior (PA) unless marked AP to denote that they are anteroposterior |
| **Lung fields** | Equal translucency?<br>Check horizontal fissure from right hilum to sixth rib at the anterior axillary line<br>Masses? Consolidation? Cavitation? |
| **Lung apices** | Check behind the clavicles. Masses? Consolidation? Cavitation? |
| **Trachea** | Central (midway between the clavicular heads)?<br>Paratracheal mass? Goitre? |
| **Heart** | Normal shape?<br>Cardiothoracic ratio (should be < half the intrathoracic diameter)<br>Retrocardiac mass? |
| **Hila** | Left should be higher than right<br>Shape (should be concave laterally; if convex, consider mass or lymphadenopathy)?<br>Density? |
| **Diaphragm** | Right should be higher than left<br>Hyperinflation (no more than 10 ribs should be visible posteriorly above the diaphragm)? |
| **Costophrenic angles** | Acute and well defined (pleural fluid or thickening, if not)? |
| **Soft tissues** | Breast shadows in females<br>Chest wall for masses or subcutaneous emphysema |
| **Bones** | Ribs, vertebrae, scapulae and clavicles<br>Any fracture visible at bone margins or lucencies? |




The normal chest X-ray. The lung markings consist of branching and tapering lines radiating out from the hila. Where airways and vessels turn towards the film, they can appear as open or filled circles (see upper pole of right hilum). The scapulae may overlie the lung fields; trace the edge of bony structures to avoid mistaking them for pleural or pulmonary shadows. To check for hyperinflation, count the ribs; if more than 10 are visible posteriorly above the diaphragm, the lungs are hyperinflated.

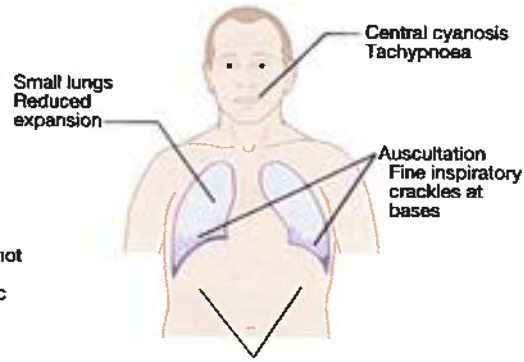
# Comparison between common chest conditions

## Chronic obstructive pulmonary disease


Pursed lip breathing
Central cyanosis
Prolonged expiration
Reduced cricosternal distance
Use of accessory muscles
Intercostal indrawing during inspiration
Hyperinflated 'barrel' chest
Cardiac apex not palpable
Loss of cardiac dullness on percussion
Auscultation
Reduced breath sounds – wheeze
Heart sounds loudest in epigastrium
Inward movement of lower ribs on inspiration (low flat diaphragm)

Also: raised jugular venous pressure (JVP), peripheral oedema from salt and water retention and/or cor pulmonale

## Pulmonary fibrosis




Also: finger clubbing common in idiopathic pulmonary fibrosis; raised JVP and peripheral oedema if cor pulmonale

## Right middle lobe pneumonia

Obscures R heart border on X-ray

Inspection
Tachypnoea
Central cyanosis (if severe)
Palpation
↓Expansion on R
Percussion
Dull R mid-zone and axilla
Auscultation
Bronchial breath sounds and ↑vocal resonance over consolidation and whispering pectoriloquy
Pleural rub if pleurisy

## Right upper lobe collapse

X-ray
Deviated trachea (to R)
Elevated horizontal fissure
↓Volume R hemithorax
Central (hilar) mass may be seen

Inspection
↓Volume R upper zone
Palpation
Trachea deviated to R
↓Expansion R upper zone
Percussion
Dull R upper zone
Auscultation
↓Breath sounds with central obstruction

## Right pneumothorax

Inspection
Tachypnoea (pain, deflation reflex)
Palpation
↓Expansion R side
Percussion
Resonant or hyper-resonant on R
Auscultation
Absent breath sounds on R

Tension pneumothorax also causes
Deviation of trachea to opposite side
Tachycardia and hypotension

## Large right pleural effusion

Inspection
Tachypnoea
Palpation
↓Expansion on R
Trachea and apex may be moved to L
Percussion
Stony dull
R mid- and lower zones
Auscultation
Absent breath sounds and vocal resonance R base
Bronchial breathing or crackles above effusion

# Oxygen dissociation curve

The oxygen dissociation curve describes the relationship between the **percentage of saturated haemoglobin** and **partial pressure of oxygen** in the blood. It is **not affected by haemoglobin concentration**.

## Basics:

- Shifts to right = for given oxygen tension there is reduced saturation of Hb with oxygen i.e. **enhanced oxygen delivery to tissues.**
- Shifts to left = for given oxygen tension there is increased saturation of Hb with oxygen i.e. **decreased oxygen delivery to tissues**

| Shifts to Left = Lower oxygen delivery | Shifts to Right = Raised oxygen delivery |
|---|---|
| HbF, Methaemoglobin, Carboxyhaemoglobin<br>Low [H+] (alkali)<br>Low PCO2<br>Low 2,3-DPG<br>Low temperature | Raised [H+] (acidic)<br>Raised PCO2<br>Raised 2,3-DPG*<br>**Raised temperature** |

**Oxygen dissociation curve:**

- Shifts **L**eft - **L**ower oxygen delivery - **L**ower acidity, temp, PCO2, 2-3 DPG - also HbF, carboxy/methaemoglobin.
- Shifts **R**ight - **R**aised oxygen delivery - **R**aised acidity, temp, PCO2, 2-3 DPG

**The L rule**

Shifts to **L** → **L**ower oxygen delivery, caused by:

- **L**ow [H+] (alkali)
- **L**ow pCO2
- **L**ow 2,3-DPG (2,3-diphosphoglycerate)
- **L**ow temperature

Another mnemonic is '**CADET**, face **Right!**' for **C**O2, **A**cid, 2,3-**D**PG, **E**xercise and **T**emperature.

# Transfer factor

## Transfer factor of the lung for carbon monoxide (TLCO)

- The transfer factor describes the rate at which a gas will **diffuse** from alveoli into blood.
- **Carbon monoxide (CO)** is used to test **the rate of diffusion.**
- Results may be given as the total gas transfer **(TLCO)** or that corrected for lung volume (transfer coefficient, **KCO)**
- **TLCO** = Lung CO transfer factor
- **KCO**= CO transfer coefficient (ml/m/mm Hg)

| Causes of a raised TLCO (4): | Causes of a lower TLCO |
|---|---|
| • **Asthma.**<br>• **Pulmonary haemorrhage: (Wegener's, Goodpasture's).**<br>• **Left-to-right cardiac shunts.**<br>• **Polycythaemia.**<br>• Male gender,<br>• **Exercise.**<br>• Hyperkinetic states. | • Pulmonary fibrosis<br>• Pneumonia<br>• Pulmonary emboli<br>• Pulmonary oedema<br>• Emphysema<br>• Anaemia<br>• Low cardiac output<br>• Sarcoidosis |

**Transfer factor:**

- **Raised**>>>> **Asthma**, Hge, Left-to-right **shunts**, **Polycythaemia.**
- **Low** >>>> everything else.

**NB:**

- Where alveolar haemorrhage occurs the TLCO tends to increase due to the enhanced uptake of carbon monoxide by intra-alveolar haemoglobin.
- KCO also tends to increase with age.
- Some conditions cause an increased KCO with a normal or reduced TLCO:
- **Pneumonectomy/lobectomy**
- **Scoliosis/kyphosis**
- **Neuromuscular weakness**
- **Ankylosis of costovertebral joints e.g. ankylosing spondylitis**

Although the conventional single breath **diffusing** capacity (DLCO) has been accepted as **a standard non-invasive test** to assess the **integrity of pulmonary function,** there are numerous pitfalls in its use.

One such pitfall is the effect of carbon monoxide in **cigarette smoke,** which raises carboxy-haemoglobin (COHb) to as high as 10-15% (normal value 1-

2%). Most regression values for DLCO are derived from the study of lifetime non-smokers, so that **the use of these in smokers underestimates** the percent of predicted DLCO values, unless additional adjustments are made.

**NB: Smoking >>> false decreasing** of DLCO values
So Smoking on the morning of the test, affects interpretation of the test.

**KCO** is the best test to confirm **restrictive** lung disease due to **parenchymal** disorder.
KCO will be **reduced** in **interstitial** lung disease.
Normal KCO would rule out significant restrictive lung disease as a cause with abnormal CT.

## Pulmonary function tests

Pulmonary function tests can be used to determine whether a respiratory disease is obstructive or restrictive.

| Obstructive lung disease | Restrictive lung disease |
|---|---|
| FEV1- significantly **reduced**<br>FVC - **reduced** or normal<br>FEV1% (FEV1/FVC)–**reduced**<br>**FEV1/FVC < 0.7** | FEV1 – **reduced**<br>FVC - significantly **reduced**<br>FEV1% (FEV1/FVC) - **normal** or **increased**<br>**FEV1/FVC > 0.7** |
| ➢ Asthma<br>➢ COPD<br>➢ Bronchiectasis<br>➢ Bronchiolitis obliterans | ➢ Pulmonary haemorrhage<br>➢ Pulmonary fibrosis<br>➢ Asbestosis<br>➢ Sarcoidosis (↓ KCO)<br>➢ Acute respiratory distress syndrome<br>➢ Infant respiratory distress syndrome<br>➢ Neuromuscular disorders<br>➢ Kyphoscoliosis e.g. ankylosing spondylitis<br>➢ Obesity<br>➢ Pneumonectomy |

In restrictive lung disease due to respiratory muscle weakness the lung itself can function normally but muscle weakness will result in grossly **low** lung volumes including forced expiratory volume in one second (FEV1), forced vital capacity (FVC) and total lung capacity (TLC).

However (RV) will be relatively high as a consequence of this weakness.

Consequently, RV/TLC will be elevated.

In **restrictive** lung disease >>> **Low VC, low TLC, high RV/TLC**

**NB:** In any patient with **FEV1 below 1** >>> there is high risk of **pneumothorax** if tried for **pleural tapping of effusion**, unless do under CT guidance. So **bronchoscopy** will be hopefully.

## Flow volume loop

A normal flow volume loop is often described as a 'triangle on top of a semi-circle'
Flow volume loops are the most suitable way of assessing **compression** of the **upper** airway e.g. in **thyroid goiter or cancer**.

This may be present in up to 40% of patients with retrosternal goitre and **generally requires at least 50% obstruction of the airway before symptoms arise.**

Flow volume loop is the investigation of choice for **upper airway compression.**

## Atelectasis

Atelectasis is a common postoperative complication in which basal alveolar collapse can lead to respiratory difficulty.
It is caused when airways become obstructed by bronchial secretions.

### Features

- it should be suspected in the presentation **of dyspnoea and hypoxaemia around 72 hours postoperatively**

### Management

- positioning the patient upright
- chest physiotherapy: breathing exercises

# Altitude related disorders

There are three main types of altitude-related disorders:
acute mountain sickness (AMS), which may progress to high altitude pulmonary oedema (HAPE) or high altitude cerebral oedema (HACE).
All three conditions are due to the chronic hypobaric hypoxia which develops at high altitudes

Acute mountain sickness is generally a self-limiting condition.

Features of AMS start to occur above 2,500 - 3,000m, developing gradually over 6-12 hours and potentially last a number of days:

- headache
- nausea
- fatigue

## Prevention and treatment of AMS

- the risk of AMS may actually be positively correlated to physical fitness
- gain altitude at no more than 500 m per day
- **acetazolamide (a carbonic anhydrase inhibitor)** is widely used to prevent AMS and has a supporting evidence base
    - it causes a primary metabolic acidosis and compensatory respiratory alkalosis which increases respiratory rate and improves oxygenation
- treatment: descent

A minority of people above 4,000m go onto develop high altitude pulmonary oedema (HAPE) or high-altitude cerebral oedema (HACE), potentially fatal conditions.

- HAPE presents with classical pulmonary oedema features
- HACE presents with headache, ataxia, papilloedema

## Management of HACE

- descent
- dexamethasone

## Management of HAPE

- descent
- nifedipine, dexamethasone, acetazolamide, phosphodiesterase type V inhibitors*
- oxygen if available

# Asthma

## Features

- worsening dyspnea, wheeze and cough that is not responding to salbutamol
- maybe triggered by a respiratory tract infection.

## Example of features used to assess asthma:

| Increase possibility of asthma | Decrease possibility of asthma |
|---|---|
| ➢ **Wheeze** breathlessness, chest **tightness** and cough, worse at night/early morning.<br>➢ **Nocturnal** cough or wheeze<br>➢ Symptoms after exercise<br>➢ Allergen exposure<br>➢ Beta blockers or aspirin.<br>➢ History of **atopic** disorder. **(Eczema)** in family.<br>➢ Wheeze heard on auscultation.<br>➢ Unexplained peripheral blood **eosinophilia.** | ➢ Prominent dizziness, light-headedness, peripheral **tingling.**<br>➢ Chronic productive cough in the absence of wheeze or breathlessness.<br>➢ Repeatedly normal physical examination.<br>➢ Significant smoking history (i.e. > 20 pack-years).<br>➢ Normal PEF or Spirometry when symptomatic. |

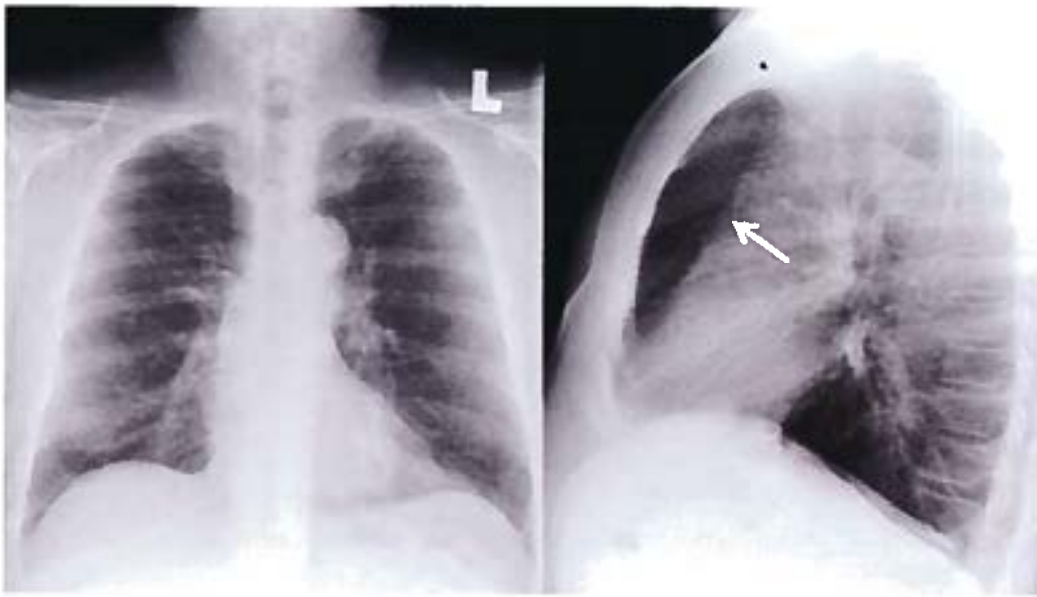
- **The 2017 British Thoracic Society (BTS) guidelines and 2019 SIGN guidelines makes a subtle change in the approach to diagnosing asthma.**
- **This approach is supported in the updated 2020 guidelines with allowance of more rescue doses of steroids in children and young people.**
- It suggests dividing patients into a **high**, **intermediate** and **low probability** of having asthma based on the presence or absence of typical symptoms.
- **The new BTS guidelines take a more practical approach to diagnosing asthma.**
- If a patient has typical symptoms of asthma a trial of treatment is recommended.

Asthma diagnosis >>> if high probability of asthma >>> start treatment

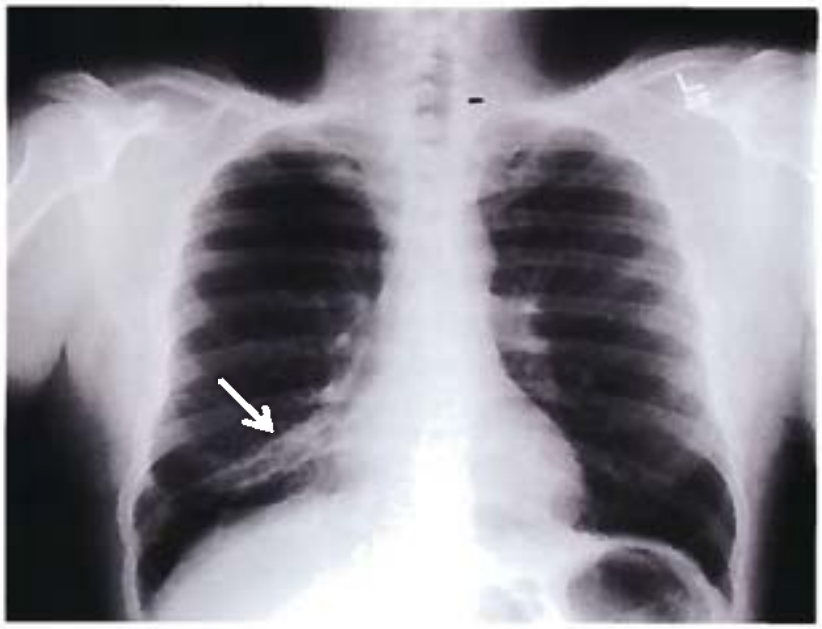
## Diagnosis:

- Compare the results of diagnostic tests undertaken whilst a patient is asymptomatic with those undertaken when a patient is symptomatic to detect variation over time.
- Carry out quality-assured spirometry using the lower limit of normal to demonstrate airway obstruction, provide a baseline for assessing response to initiation of treatment and exclude alternative diagnoses.
- **Obstructive spirometry with positive bronchodilator reversibility increases the probability of asthma.**
- **Normal spirometry in an asymptomatic patient does not rule out the diagnosis of asthma.**
- Undertake a structured clinical assessment to assess the initial probability of asthma. This should be based on:
- **history** of recurrent episodes (attacks) of symptoms, ideally corroborated by variable peak flow when symptomatic and asymptomatic
- **symptoms** of wheeze, cough, breathlessness and chest tightness that vary over time
- recorded observation of wheeze heard by a healthcare professional
- personal/family history of other atopic conditions (in particular, atopic eczema/dermatitis, allergic rhinitis)
- no symptoms/signs to suggest alternative diagnoses.

Patient with severe asthma, atopic dermatitis, and allergic rhinitis—atopic triad.



Acute asthma exacerbation with increased lung volumes on chest X-ray. The lateral projection reveals enlargement of the retrosternal clear space (*arrow*).



Acute asthma exacerbation in a 28-year-old man. Frontal chest radiograph demonstrates increased lung volumes and ill-defined opacity in the right infra-hilar region consistent with middle lobe segmental atelectasis (*arrow*).

Dust mites under the microscope. Dust mites are a common allergen for patients who suffer from asthma and allergic rhinitis. Environmental control to minimize dust mite exposure can help control asthma for some individuals.

### In patients with a high probability of asthma:

- record the patient as likely to have asthma and commence a carefully monitored initiation of treatment (typically six weeks of inhaled corticosteroids)
- assess the patient's status with a validated symptom questionnaire, ideally corroborated by lung function tests **(FEV1 at clinic visits or by domiciliary serial peak flows to capture times with/without symptoms)**
- with a good symptomatic and objective response to treatment, confirm the diagnosis of asthma and record the basis on which the diagnosis was made
- if the response is poor or equivocal, check inhaler technique and adherence, arrange further tests and consider alternative diagnoses.

**There is particular emphasis on the use of fractional exhaled nitric oxide (FeNO). Nitric oxide is produced by 3 types of nitric oxide synthases (NOS). One of the types is inducible (iNOS) and levels tend to rise in inflammatory cells, particularly eosinophils.**
**Levels of NO therefore typically correlate with levels of inflammation**

- Use measurement of (fractional exhaled nitric oxide)FeNO (if available) to find evidence of eosinophilic inflammation.
- A positive test increases the probability of asthma but a negative test does not exclude asthma.
- Use a previous record of skin-prick tests, blood eosinophilia of 4% or more, or a raised allergen-specific IgE to corroborate a history of atopic status, but do not offer these tests routinely as a diagnostic test for asthma.

## Management is based on this assessment:

- **High probability: trial of treatment**
- Low probability: investigate/treat other condition
- Intermediate probability: see below

For patients with an **intermediate** probability of asthma further investigations are suggested.

The guidelines state that **Spirometry** is the preferred initial test:

- FEV1/FVC **< 0.7**: trial of treatment
- FEV1/FVC **> 0.7**: further investigation/consider referral
- Recent studies have shown the limited value of other 'objective' tests.
- It is now recognised that in patients with normal or near-normal pre-treatment lung function there is little room for measurable improvement in FEV1 or peak flow.> 400 ml improvement in FEV1 is considered significant before and after 400 mcg inhaled salbutamol in patients with diagnostic uncertainty and airflow obstruction present at the time of assessment.

if there is an incomplete response to inhaled salbutamol, **OFFER** either inhaled corticosteroids (200 mcg twice daily beclomethasone equivalent for 6-8 weeks) or oral prednisolone (30 mg once daily for 14 days) to check reversibility.

It is now advised to interpret **peak flow** variability with caution due to the **poor sensitivity** of the test

- Diurnal variation % = [(Highest - Lowest PEFR) / Highest PEFR] x 100
- Assessment should be made over 2 weeks
- Greater than 20% diurnal variation is considered significant

**Diurnal variation** of peak expiratory flow rate (**PEFR**) **greater than 20%** is one of the diagnostic criteria for asthma.

**IgE** being elevated is non-specific, but can suggest an atopic phenotype.

Skin prick tests can confirm allergy, but this does not necessarily mean the patient will develop asthma.

- **Inhaled corticosteroids** are the recommended preventer drug for adults and children for achieving overall treatment goals.
- Inhaled corticosteroids should be considered for adults, children aged 5–12 and children under the age of five with any of the following features: using inhaled β2 agonists three times a week or more; symptomatic three times a week or more; or waking one night a week. In addition, ICS should be considered in adults and children aged 5–12 who have had an asthma attack requiring oral corticosteroids in the last two years .(2019)

**The first choice as add-on therapy to inhaled corticosteroids in adults is an inhaled long-acting β2 agonist,** which should be considered before increasing the dose of inhaled corticosteroid.

B In children aged five and over, an inhaled long-acting β2 agonist or a leukotriene receptor antagonist can be considered as initial add-on therapy.
**If asthma control remains suboptimal after the addition of an inhaled long-acting β2 agonist then:**

- increase the dose of inhaled corticosteroids from low dose to medium dose in adults or from very low dose to low dose in children (5–12 years), if not already on these doses. or
- consider adding a leukotriene receptor antagonist

**Tiotropium bromide A review of RCTs in adults taking tiotropium bromide, a long-acting muscarinic antagonist (LAMA), in addition to ICS plus LABA compared with ICS plus LABA, reported fewer asthma exacerbations (although results were inconclusive), improved lung function and some benefits relating to asthma control in those taking tiotropium, but no improvement in quality of life.**

- Evidence relating to serious adverse effects was inconclusive but fewer non-serious adverse events were reported in those taking tiotropium.
- In two of the three trials included in the review patients were taking high-dose ICS.481 The addition of tiotropium to high-dose ICS plus LABA may confer some additional benefit although results are currently inconclusive.
- Further research is needed to confirm possible benefits or harms of tiotropium in combination with different doses of ICS/LABA.

**If asthma control remains inadequate on medium-dose (adults) or low-dose (children) of inhaled corticosteroid plus a long-acting β2 agonist or a leukotriene receptor antagonist,** the following interventions can be considered:

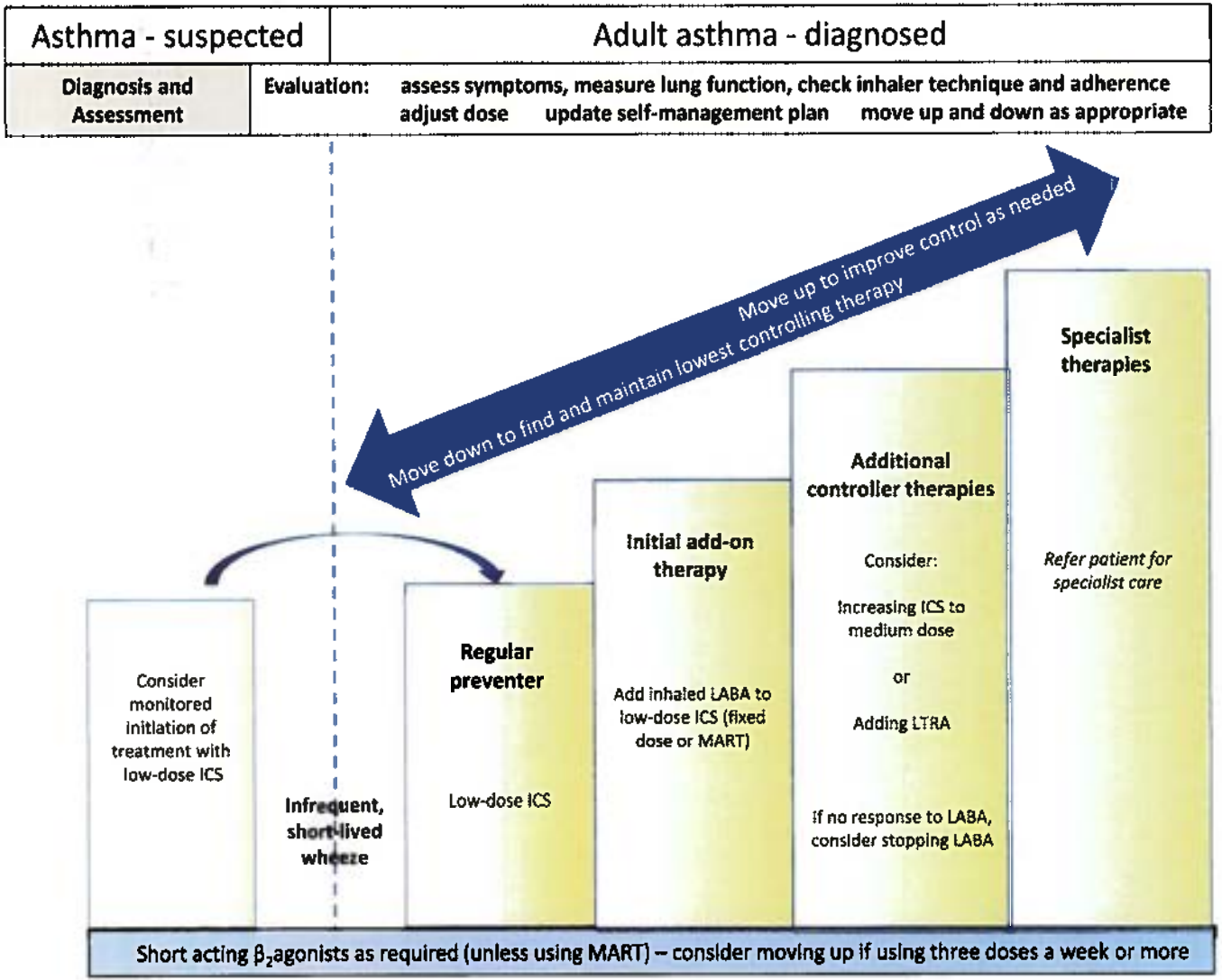
- increase the inhaled corticosteroids to high dose (adults)/ medium dose (children 5–12 years)* or
- add a leukotriene receptor antagonist (if not already trialled) or
- add tiotropium (adults) or
- add a theophylline.

Omalizumab given by subcutaneous injection may be considered in eligible patients with a high oral corticosteroid burden.
A Mepolizumab (subcutaneous), reslizumab (intravenous) and benralizumab (subcutaneous) may be considered in eligible patients with a high oral corticosteroid burden (2020)

## Summary of:

Stepwise management of stable asthma in adults (a step-wise approach):

| Step | Management |
|---|---|
| **Step 1** | Inhaled **short-acting B2 agonist** (SABA) PRN (e.g. salbutamol PRN) |
| **Step 2** | • Add **Inhaled Corticosteroid (ICS)** at 200-800 mcg/day (beclometasone dipropionate or **fluticasone).**<br>• 400 mcg is an appropriate starting dose for many patients.<br>• Start at dose of inhaled steroid appropriate to severity of disease. If no good response. **according to BTS you can add here leukotriene receptor antagonist (LTRA)** |
| **Step 3** | 1. Add **inhaled long-acting B2 agonist (LABA):** (e.g. Salmeterol 50mg/d or formoterol)<br>2. Assess control of asthma:<br>• **Good** response to LABA >>> continue LABA<br>• **Partial** response i.e. benefit from LABA but **control still inadequate** >>> continue LABA and increase ICS dose to 800 mcg/day (if not already on this dose).<br>• **No** response to LABA >>> stop LABA + increase ICS inhaled steroid to 800 mcg/ day + institute trial of other therapies, leukotriene receptor antagonist or SR theophylline. **(If you already started on LTRA Continue LTRA depending on patient's response to LTRA)** |
| **Step 4** | **Consider trials of:**<br>• **Increasing inhaled steroid** up to 2000 mcg/day<br>• Addition of **a fourth drug** e.g. Leukotriene receptor antagonist, SR theophylline, B2 agonist tablet.<br>• SEEK EXPERT ADVICE |
| **Step 5** | • Use **daily steroid tablet** in lowest dose providing adequate control.<br>• Consider other treatments to minimise the use of steroid tablets.<br>• **Maintain high dose inhaled steroid at 2000 mcg/day.**<br>• **Refer patient for specialist care.** |


Asthma - suspected
Adult asthma - diagnosed
Diagnosis and Assessment
Evaluation: assess symptoms, measure lung function, check inhaler technique and adherence
adjust dose update self-management plan move up and down as appropriate
Move up to improve control as needed
Move down to find and maintain lowest controlling therapy
Consider monitored initiation of treatment with low-dose ICS
Infrequent, short-lived wheeze
Regular preventer
Low-dose ICS
Initial add-on therapy
Add inhaled LABA to low-dose ICS (fixed dose or MART)
Additional controller therapies
Consider:
Increasing ICS to medium dose
or
Adding LTRA
If no response to LABA, consider stopping LABA
Specialist therapies
Refer patient for specialist care
Short acting β2agonists as required (unless using MART) – consider moving up if using three doses a week or more

## Additional notes:

### Leukotriene receptor antagonists:

- e.g. **Montelukast, zafirlukast**
- Have **both** anti-inflammatory and bronchodilatory properties.
- Should be used when patients are poorly controlled on high-dose inhaled corticosteroids (ICS) and a long-acting b2-agonist (LABA).
- Particularly useful in aspirin-induced asthma.
- Associated with development / worsening of Churg-Strauss syndr

**the definitions of what constitutes a low, moderate or high-dose ICS have also changed. For adults:**

| | |
|---|---|
| **Low Dose** | <= 400 micrograms budesonide or equivalent |
| **Moderate Dose** | 400 micrograms - 800 micrograms budesonide or equivalent |
| **High Dose** | > 800 micrograms budesonide or equivalent |

- Fluticasone is more lipophilic and has a longer duration of action than beclometasone also it is roughly twice as potent as beclometasone.
- Hydrofluoroalkane is now replacing chlorofluorocarbon as the propellant of choice. Only half the usually dose is needed with hydrofluoroalkane due to the smaller size of the particles.
- LABA) Long acting B2-agonists acts as bronchodilators but also inhibit mediator release from mast cells. Recent meta-analysis showed **adding salmeterol improved symptoms compared to doubling the inhaled steroid dose.**
- **Salmeterol** has been reported to produce **an acute exacerbation of asthma**, possibly through **an acute hypersensitivity reaction** ☹
- **Seretide Discus®** = Salmeterol 50 mg+ Fluticasone 250 or 500 Mcg

- Both the British National Formula (BNF) and British Thoracic Society (BTS) guidelines stress the need for **good control of asthma during pregnancy.**
- The BTS guidelines make it clear that short-acting /long-acting beta 2-agonists, inhaled and oral corticosteroids should all be used **as normal during pregnancy.**
- The BNF advises that 'inhaled drugs, theophylline and prednisolone can be taken **as normal during pregnancy and breast-feeding.**

# Leukotriene receptor antagonists

## Basics

- e.g. Montelukast, zafirlukast
- have both anti-inflammatory and bronchodilatory properties
- should be used when patients are poorly controlled on high-dose inhaled corticosteroids and a long-acting b2-agonist
- particularly useful in aspirin-induced asthma
- associated with the development of Churg-Strauss syndrome

# Omalizumab

Omalizumab is a new drug that is available for the management of severe asthma. As it's name suggests it's a monoclonal antibody that specifically binds to free human immunoglobulin E (IgE).

Omalizumab is given as a subcutaneous injection every 2 to 4 weeks.

## Where does omalizumab fit into current management?

NICE updated their technology appraisal of omalizumab in 2013. A copy of the criteria is given below. The emphasis in bold has been added.

Omalizumab is recommended as an option for treating **severe persistent confirmed allergic IgE-mediated asthma** as an **add on to optimised standard therapy** in people **aged 6 years and older**:

- who need continuous or frequent treatment with **oral corticosteroids (defined as 4 or more courses in the previous year)**

Optimised standard therapy is defined as a full trial of and, if tolerated, documented compliance with inhaled high-dose corticosteroids, long-acting beta agonists, leukotriene receptor antagonists, theophyllines, oral corticosteroids, and smoking cessation if clinically appropriate.

## Adverse effects

- abdominal pain
- headache
- fever
- Churg-Strauss syndrome: may present with eosinophilia, vasculitic rash, worsening respiratory symptoms and peripheral neuropathy

# Acute severe asthma

Acute severe asthma are stratified into moderate, severe or life-threatening:

| Moderate | Acute Severe | Life-threatening |
|---|---|---|
| ➢ **PEFR** > 50% best or predicted.<br>➢ **Speech** normal.<br>➢ **RR** < 25 / min<br>➢ **Pulse** < 110 bpm. | ➢ PEFR 33 - 50% best or predicted.<br>➢ Can't complete sentences.<br>➢ RR > 25/min.<br>➢ Pulse > 110 bpm. | ➢ **PEFR < 33%** best or predicted.<br>➢ **Oxygen sat < 92%.**<br>➢ 'Normal' pC02 (4.6-6.0 kPa)<br>➢ Silent chest, cyanosis or feeble respiratory effort.<br>➢ Bradycardia, dysrhythmia or hypotension.<br>➢ Exhaustion, confusion or coma. |

**Indications** of life threatening asthma by the guidelines, these are:

- PEFR <33% best or predicted
- $SpO_2$ <92%
- $PaO_2$ <8 kPa
- **Normal $PaCO_2$** (4.5-6.0 kPa)
- Silent chest
- Cyanosis
- Poor respiratory effort
- Arrhythmia
- Exhaustion, or
- Altered conscious level.

Asthma + **normal** or **low PCO2** >>> **Life threatening asthma,** it is a warning of impending respiratory failure as the patient becomes too tired to ventilate adequately.

The BTS defines **near fatal asthma** as an attack with **raised PCO2** and/or **requiring mechanical ventilation** with raised inflation pressures.
A raised PaCO2 is an important sign that **intubation** may be required if the patient is not responding to maximum medical management.

Non-invasive ventilation is not recommended in acute severe asthma

**Acute severe asthma** >>> acute respiratory alkalosis with associated hypoxia (Hypoxia ↓PO2, ↓PCO2, alkalosis ↑PH).

**Other D.D of Hypoxia, Hypocapnia, Alkalosis:**

1) **Acute severe asthma.**
2) **Pulmonary embolism.**
3) **Anxiety hyperventilation syndrome** (but **NO** Hypoxia).

## British Thoracic Society (BTS) guidelines:

- **admission**
  - all patients with life-threatening should be admitted in hospital
  - patients with features of severe acute asthma should also be admitted if they fail to respond to initial treatment.
  - other admission criteria include a previous near-fatal asthma attack, pregnancy, an attack occurring despite already using oral corticosteroid and presentation at night
- **Beta 2-agonists** should be administered as soon as possible, preferably **nebulised driven by oxygen**.
- Repeat doses should be given at 15–30-minute intervals, or **continuous nebulisation** can be used where there is inadequate response to bolus therapy.
- **Nebulised ipratropium bromide** should be added for patients with acute severe or life-threatening asthma, or those with a poor initial response. Its addition produces significantly greater bronchodilation than a β2-agonist alone.
- **Oxygen** should be given to maintain saturations at **94-98%.** Patients with saturations **less than 92% on room air** should have an **ABG** to exclude hypercapnia.
- However, starting treatment should not be delayed to do the ABG. **Initially high-flow oxygen is used**, and then weaned to maintain adequate saturations.
- Unless you suspect COPD there isn't a need to be cautious with oxygen therapy.
- **Steroids** reduce mortality, relapses, subsequent hospital admission and requirement for β2-agonists.
- The earlier they are given in the attack, the better the outcome.
- A dose of **40-50mg** should therefore be given once oxygen and nebuliser therapy has been established.
- This should be continued **for 5 days, or until recovery**, and can then be **stopped abruptly unless** the patient has taken long-term oral corticosteroids.
- **Magnesium sulphate (MgSo4) IV** recommended as next step for patients who are not responding to SOS (Salbutamol inhalation + Oxygen + Steroids) (e.g. 2g IV over 20 mins).
- The mechanism by which it has its effect is not fully understood, but it is thought that low magnesium levels in bronchial smooth muscle favour bronchoconstriction.
- The **RR should be over 25 breaths/min** in a patient with severe asthma who was not yet showing signs of respiratory fatigue.

- **IV aminophylline** may be considered following consultation with senior medical staff
- **patients who fail** to respond require senior critical care support and should be treated in an appropriate ITU/HDU setting. Treatment options include:
  - intubation and ventilation
  - extracorporeal membrane oxygenation (ECMO)

## Occupational Asthma:

Episodic cough and wheeze with nocturnal symptoms are classical of asthma.

Occupational asthma is the commonest industrial lung disease with over 400 causes and accounts for **up to 10% of adult-onset asthma**.

There are an estimated 1500 to 3000 cases of occupational asthma reported each year.

The commonest occupations affected are spray painters, bakers, chemical processors, plastics workers and welders and soldering.

Patients are **characteristically better when on holiday.**

## Causes:

- **Isocyanate's cobalt - the most common cause**. Example occupations include spray painting and foam moulding using adhesives.
- **Platinum salts**
- **Soldering flux resin**
- Epoxy resins
- **Flour**
- Formaldehyde, Glutaraldehyde, and Chlorhexidine.
- Proteolytic enzymes

## Diagnosis:

**Serial measurements** of peak expiratory flow rate **(PEFR)** are recommended both at **work** and **away from work.**
Recordings should be performed **two hourly for 4 weeks** or if this is not possible meta-choline/histamine challenges can be undertaken after days at work and away from work.
Bronchial provocation testing should only be undertaken is a specialized centre.

### Treatment

- The most appropriate treatment firstly to **review of the work environment** to ensure that exposure to paint fumes are minimised.
- If these changes do not improve his symptoms, then he **should be offered alternative work (change the job).**

### Nocturnal asthma

**EX:** female patient 25 years old has 10 months history of **nocturnal cough** and SOB, particularly first thing in the **morning**, chest wheezes, she has **GERD**, not smoker, Vitally stable, Normal CXR, **low PEFR**.

**Treatment:**

- **Regular low dose inhaled steroids (Betamethasone).**
- Previously was PPI and head elevation at bedtime.

### Exercise-induced asthma

It is best diagnosed with **spirometry before and after exercise**, where a typical obstructive pattern may be displayed following exercise.

No abnormalities may be displayed following bronchodilator therapy if it is true exercise-induced asthma. Similarly lung volumes and diffusion capacity are likely to be unaffected.

Blood gas analysis would be relatively unhelpful in this scenario as little change in partial pressures would be expected.

## Pulmonary eosinophilia

### Causes of pulmonary eosinophilia:

- Churg-Strauss syndrome
- Allergic Broncho pulmonary aspergillosis (ABPA)
- Loffler's syndrome
- Eosinophilic pneumonia
- Hypereosinophilic syndrome
- Tropical pulmonary eosinophilia
- Drugs: nitrofurantoin, sulphonamides
- Less common: Wegener's granulomatosis

# Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome) (CSS)

Churg-Strauss syndrome is a **rare** vasculitis, it is an **ANCA** associated **small-medium** vessel vasculitis.
Incidence is approximately 2.5 cases per 100,000 adults per year.

The typical picture of a patient with CCS is asthma, allergic rhinitis, raised eosinophilic count and eosinophilic vasculitis, mild renal impairment, microscopic haematuria and raised IgE.

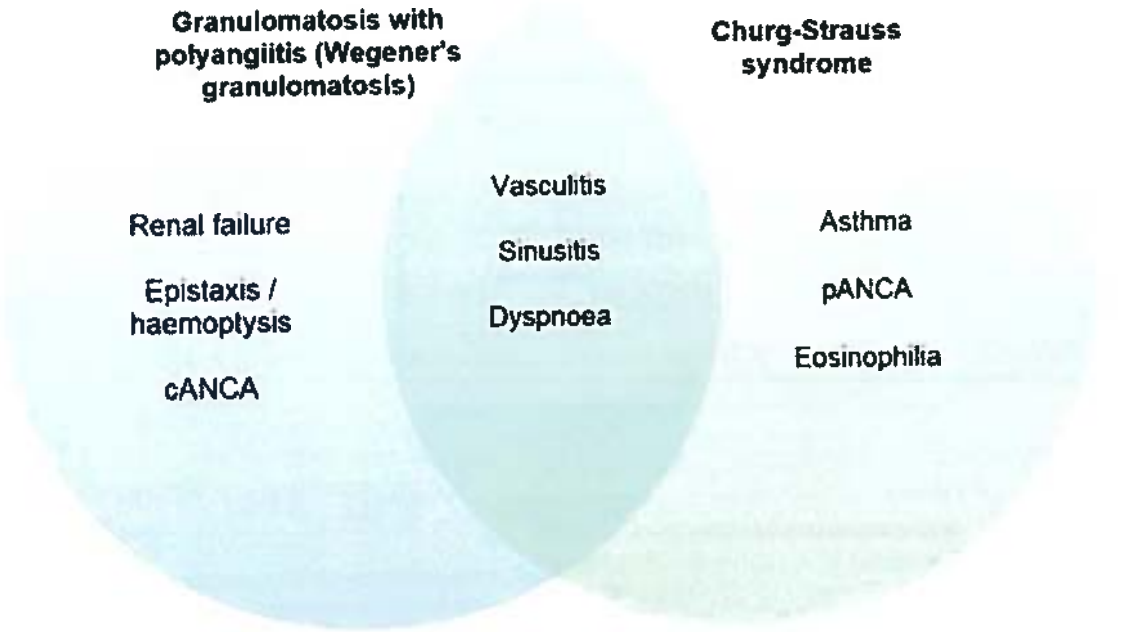
Asthma + Eosinophilia + Renal imp + Microscopic Haematuria + Nerve lesion **>>> CSS**

## Features:

- **Asthma**
- Blood **eosinophilia** (e.g. **> 10%)**
- **Paranasal sinusitis** or abnormal growths (polyps).
- **Non- fixed Pulmonary infiltrates** (may be **transient)**
- **Histological proof** of vasculitis with **extravascular eosinophils by vascular biopsy**.
- **Mononeuritis multiplex** occurs **75%** of patients (e.g. ulnar nerve palsy with foot drop) or **polyneuropathy.**
- **pANCA** positive in **60%,** but their presence or absence is not diagnostic.
- Serum IgE is very commonly elevated and correlates with disease severity.
- **Rarely,** it can cause either an anterior or a posterior ischaemic optic neuropathy, which presents with **visual loss.**
- **Nephritic syndrome**: **hypertension**, **oedema** and **haematuria.**

**ACR criteria** for the diagnosis of Churg-Strauss syndrome requires **4** of the following features:

- Asthma
- Eosinophilia greater than 10%
- Paranasal sinus abnormality
- **Non-fixed** pulmonary infiltrates visible on chest radiographs
- Sensory mononeuropathy or polyneuropathy and
- Blood vessels biopsy with extravascular eosinophils.




- Mainly due to myocarditis and MI secondary to coronary arteritis.
- With treatment the 1-year survival rate is 90% and the 5-year survival rate is 62%.
- Overall, without tratment the 5-year survival rate is 25%.

## Treatment:

- **Glucocorticoids alone** usually are adequate.
- Immunosuppressant drugs (cyclophosphamide, azathioprine, MMF) are necessary in fewer than 20% of patients.
- Pulse steroid IV may be required in major life-threatening organ involvement.
- Others: IVIG, IFN-alpha and plasma exchange (debatable).

**NB**: Leukotriene receptor antagonists may precipitate the disease.

# Drugs used in respiratory medicine

## Drugs used in respiratory medicine

| Drug | Mechanism of action | Notes |
|---|---|---|
| **Salbutamol** | Beta receptor agonist | • Short-acting inhaled bronchodilator. Relaxes bronchial smooth muscle through effects on beta 2 receptors<br>• Used in asthma and chronic obstructive pulmonary disease (COPD).<br>• Salmeterol has similar effects but is long-acting |
| **Corticosteroids** | Anti-inflammatory | • Inhaled corticosteroids are used as mainterance therapy<br>• Oral or intravenous corticosteroids are used following an acute exacerbation of asthma or COPD |
| **Ipratropium** | Blocks the muscarinic acetylcholine receptors | • Short-acting inhaled bronchodilator. Relaxes bronchial smooth muscle<br>• Used primarily in COPD<br>• Tiotropium has similar effects but is long-acting |
| **Methylxanthines (e.g. theophylline)** | Non-specific inhibitor of phosphodiesterase resulting in an increase in cAMP | • Given orally or intravenously<br>• Has a narrow therapeutic index |
| **Monteleukast, zafirlukast** | Blocks leukotriene receptors | • Usually taken orally<br>• Useful in aspirin-induced asthma |

## Microscopic polyangiitis

Microscopic polyangiitis is a small-vessel ANCA vasculitis.

### Features

- renal impairment: raised creatinine, haematuria, proteinuria
- fever
- other systemic symptoms: lethargy, myalgia, weight loss
- rash: palpable purpura
- cough, dyspnoea, haemoptysis
- mononeuritis multiplex

### Investigations

- pANCA (against MPO) - positive in 50-75%
- cANCA (against PR3) - positive in 40%

## Granulomatosis with polyangiitis

Granulomatosis with polyangiitis is now the preferred term for Wegener's granulomatosis. It is an autoimmune condition associated with a necrotizing granulomatous vasculitis, affecting both the upper and lower respiratory tract as well as the kidneys.

### Features

- upper respiratory tract: epistaxis, **sinusitis,** nasal crusting
- lower respiratory tract: dyspnoea, **haemoptysis**
- **rapidly progressive glomerulonephritis** ('pauci-immune', 80% of patients)
- **saddle-shape nose deformity**
- also: vasculitic rash, eye involvement (e.g. proptosis), cranial nerve lesions.

### Investigations

- cANCA positive in > 90%, pANCA positive in 25%
- chest x-ray: wide variety of presentations, including cavitating lesions
- renal biopsy: **epithelial crescents in Bowman's capsule**

### Management

- steroids
- cyclophosphamide (90% response)
- plasma exchange
- median survival = 8-9 years

Chest x-ray from a young patient with granulomatosis with polyangiitis. Whilst the changes are subtle it demonstrates a number of ill-defined nodules the largest of which projects over the dome of the right hemidiaphragm. This nodule appears to have a central lucency suggesting cavitation

CT of the same patient showing the changes in a much more obvious way, confirming the presence of at least 2 nodules, the larger of the two having a large central cavity and and air-fluid level

## Loffler's syndrome

- Transient CXR shadowing and blood eosinophilia.
- Thought to be due to parasites such as Ascaris lumbricoides causing an alveolar reaction.
- There is fever, cough and night sweats which often last less than 2 wks.
- Generally,a self-limiting disease

## Tropical pulmonary eosinophilia

- Associated with Wuchereria bancrofti infection.

# Aspergillus and Aspergillosis

Aspergillus is a fungus transmitted to humans via inhalation.

Hence, it is primarily affecting the lungs, causing **5** main syndromes:

**1) Asthma**: it is type **I** hypersensitivity reaction to fungal spores.

**2) ABPA (Allergic Broncho pulmonary Aspergillosis):**

- It is type **III** hypersensitivity reaction to Aspergillus fumigatus.

**3) Aspergilloma:**

- It is a **fungal ball within a pre-existing lung cavity** that may have resulted from **TB (an old tuberculous cavity)**, sarcoidosis, or other necrotizing pulmonary process.
- It is usually asymptomatic but may cause cough, **haemoptysis** (in **75%** of cases) and fever.
- Precipitating antibodies help to confirm the diagnosis and are present in 95% of cases.

**4) Invasive aspergillosis (IA):**

- Aspergillosis is a **fungal** infection, and develops mainly in individuals who are immunocompromised.
- It typically manifests with fever, cough, dyspnoea, and pleuritic chest pain in patients with **prolonged neutropenia** or **immunosuppression**, such as that which occurs **after chemotherapy.**
- It is a leading cause of death in **acute leukaemia** and haemopoietic stem cell transplantation.
- It is caused by **haematogenous** spread of the fungus.
- CXR shows consolidation and the patient has rapidly progressing and worsening hypoxemia.
- It is often seen on CXR and CT scan, and demonstrates **an air crescent sign.**
- Definitive diagnosis is by microscopy and depends upon the demonstration of the organism in tissue.
- H&E stain does not stain most of the fungi, except the Aspergillus species and the zygomycetes.
- IA can only be confidently diagnosed by the finding of characteristic hyphae on a **biopsy** specimen.
- Other investigations include the **galactomannan test.**

**Treatment:** Liposomal Amphotericin IV 3 mg/kg or

- Voriconazole or
- Caspofungin.

EX: Male pt. 25 years old **post bone marrow transplantation** due to CML, he has **fever**, lobar pneumonia on CXR, already on **meronam** and **vancomycin**, Labs: **low TLC 0.2**, Hb 9, PLT 12, **negative** blood and urine C&S >>>? Invasive Aspergillosis (IA) for Amphotericin or Voriconazole or Caspofungin.

**Semi-invasive aspergillosis:**

It is a chronic indolent disease that affects people with **mild immunosuppression** such as those with **DM, COPD, alcoholics**, and **elderly** or on prolonged **steroid** use.

If left untreated there is a significant associated mortality; however it is **difficult to diagnose due to its slow progression** both clinically and radiologically (i.e. may be with **normal CXR**).

Symptoms includes cough, wheezes, bronchitis and **haemoptysis in 15%**.

**EX**: Pt DM, alcoholic with 1 year history of cough, expectoration, haemoptysis

## Allergic broncho-pulmonary aspergillosis (ABPA)

- It results from an allergy (hypersensitivity reaction) to Aspergillus spores.
- Immediate (type I) reactions occur in virtually all patients with ABPA following intradermal injections of **Aspergillus fumigatus** extracts, with only 16% developing delayed (type IV) reactions.
- It predominantly affects patients with **cystic fibrosis, asthma,** and **bronchiectasis.**
- It is a hypersensitivity reaction to Aspergillus in asthmatic people.
- It should always be exclude in people with asthma who have a raised eosinophil count.
- In the exam questions often give a history of **bronchiectasis** and **eosinophilia.**
- There is initially bronchospasm which can progress to **proximal bronchiectasis** and occasionally **upper** zone lung fibrosis like TB.
- Exacerbations are more common in **the autumn and winter months.**

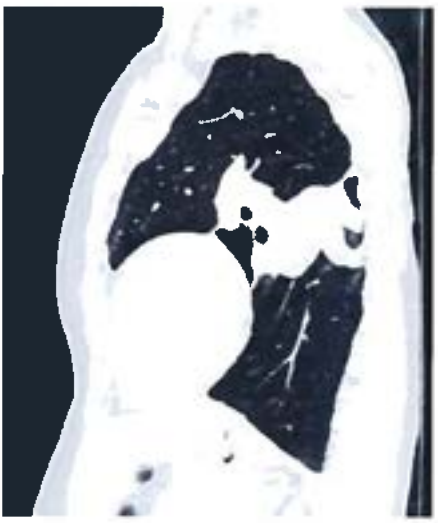
## Features:

- **Bronchoconstriction**: wheeze, cough, dyspnoea, especially in patients labelled with asthma.
- **Bronchiectasis** (proximal).

## Investigations:

- **Eosinophilia**
- Fleeting CXR changes is due to intermittent obstruction of airways.
  **Skin prick: Positive Radioallergosorbent (RAST) test to Aspergillus**
- **Positive IgG precipitins to Aspergillus** in **70%** of patients. (not as positive as in aspergilloma)
- Raised IgE

Chest x-ray of a 40-year-old woman with ABPA demonstrating a mass overlying the left hilum. In the right upper parahilar region a few ring shadow / tram track opacities are also noted, suggestive of bronchiectasis



CT scan from the same patient. CT reveals a branching lesion in the superior segment of the left lower lobe with classic finger in glove appearance which represents of mucous filling dilated bronchi (i.e. bronchocoeles). Bronchocoeles are a common feature of allergic bronchopulmonary aspergillosis (ABPA)

## Management:

- **Steroids oral**: is the mainstay of initial treatment
- **Itraconazole** is sometimes introduced as a 2nd line treatment (additional prolonged courses of itraconazole **up to 4 months** may diminish the steroid requirement).

A 36-year-old man who is a known **asthmatic** complains of persistent cough and shortness of breath, which is **unresponsive** to his normal inhaled therapy. A CXR shows **fibrosis** of both **upper** lobes. HRCT: proximal bronchiectasis.

What is the most likely diagnosis? >>> **ABPA**

## Aspergilloma

An aspergilloma is a **fungus ball** which often colonises **an existing lung cavity** (e.g. secondary to **TB**, lung cancer or cystic fibrosis).
Usually **asymptomatic** but features may include:

- **Cough**
- **Haemoptysis** (may be **severe**)

### Investigations:

- CXR containing a **rounded opacity surrounded with a rim of air.**
- **Serum high titres Aspergillus precipitins**

### Treatment:

- **Surgical resection**: is the curative ttt
- Long term Itraconazole: in patients not fit for surgery, it leads to resolution of the lesion in up to 60% of patients.
- Arterial embolization: where there is life threatening haemoptysis

# COPD

**Based on (nice guidelines last updated 26 july 2019) and global initiatives for copd (gold) guidelines 2023**

## Causes:

- **Smoking.**
- **Alpha-1 antitrypsin deficiency.**
- Other causes:
  - **Cadmium** (used in smelting)
  - **Coal**
  - **Cotton**
  - **Cement**
  - **Grain**

**NB:** Isocyanates are more associated with occupational asthma

## Symptoms:

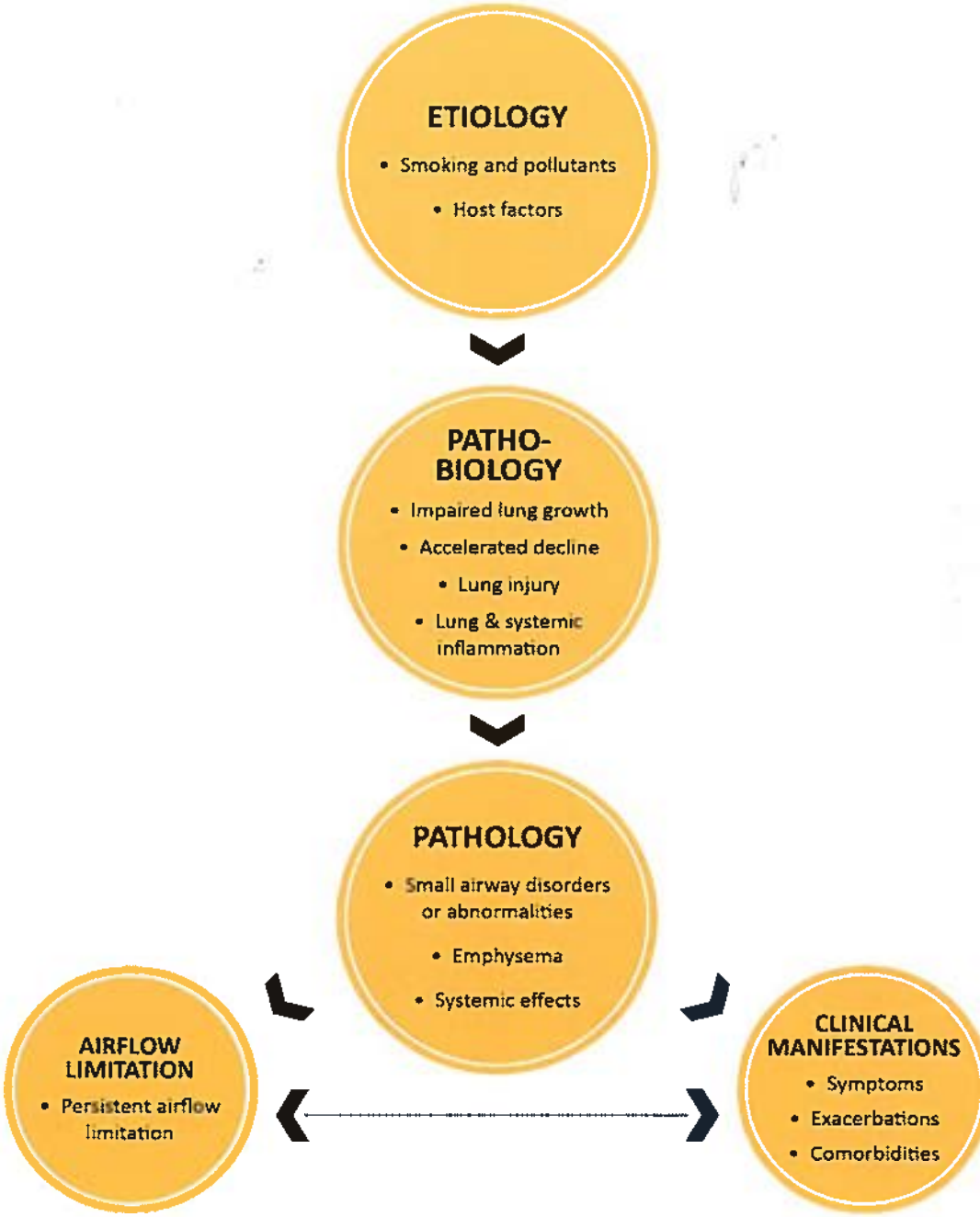
**Suspect a diagnosis of COPD in people over 35 who have a risk factor (generally smoking or a history of smoking) and who present with 1 or more of the following symptoms:**

- exertional breathlessness.
- chronic cough.
- regular sputum production.
- frequent winter 'bronchitis'
- wheeze.

**When thinking about a diagnosis of COPD, ask the person if they have:**

- weight loss
- reduced exercise tolerance
- waking at night with **breathlessness**
- ankle swelling
- fatigue
- occupational hazards
- chest pain
- hemoptysis (coughing up blood). **These last 2 symptoms are uncommon in COPD and raise the possibility of alternative diagnoses**

## ETIOLOGY, PATHOBIOLOGY AND PATHOLOGY OF COPD LEADING TO AIRFLOW LIMITATION AND CLINICAL MANIFESTATIONS



## ► KEY INDICATORS FOR CONSIDERING A DIAGNOSIS OF COPD

Consider COPD, and perform spirometry, if any of these indicators are present in an individual over age 40. These indicators are not diagnostic themselves, but the presence of multiple key indicators increases the probability of a diagnosis of COPD. Spirometry is required to establish a diagnosis of COPD.

| | |
|---|---|
| **Dyspnea that is:** | • Progressive over time.<br>• Characteristically worse with exercise.<br>• Persistent |
| **Chronic Cough:** | • May be intermittent and may be unproductive<br>• Recurrent wheeze |
| **Chronic Sputum Production:** | • Any pattern of chronic sputum production may indicate COPD |
| **Recurrent Lower Respiratory Tract Infections** | |
| **History of Risk Factors:** | • Host factors (such as genetic factors, congenital/developmental abnormalities etc.)<br>• Tobacco smoke (including popular local preparations)<br>• Smoke from home cooking and heating fuels.<br>• Occupational dusts, vapors, fumes, gases and other chemicals. |
| **Family History of COPD and/or Childhood Factors.** | • For example low birthweight, childhood respiratory infections etc. |

## ▶ DIFFERENTIAL DIAGNOSIS OF COPD

| DIAGNOSIS | SUGGESTIVE FEATURES |
|---|---|
| **COPD** | • Onset in mid-life.<br>• Symptoms slowly progresive.<br>• History of tobacco smoking or exposure to other types of smoke. |
| **Asthma** | • Onset early in life (often childhood).<br>• Symptoms vary widely from day to day.<br>• Symptoms worse at night/early morning.<br>• Allergy rhinitis, and/or eczema also present.<br>• Family history of asthma. Obesity coexistence |
| **Congestive Heart Failure** | • Chest X-ray shows dilated heart, pulmonary edema.<br>• Pulmonary function tests indicate volume restriction. not airflow limitation. |
| **Bronchiectasis** | • Large volumes of purulent sputum.<br>• Commonly associated with bacterial infection.<br>• Chest X-ray/CT shows bronchial dilation, bronchial wall thickening. |
| **Tuberculosis** | • Onset all ages.<br>• Chest X-ray shows lung infiltrate.<br>• Microbiological confirmation High local prevalence tuberculosis. |
| **Obliterative Bronchiolitis** | • Onset at younger age nonsmokers.<br>• May have history of rheumatoid arthritis or acute fumie exposure Seen after lung or bone marrow transplantation.<br>• CT on expiration shows hypodense areas. |
| **Diffuse Panbronchiolitis** | • Predominantly seen in patients of Asian descent<br>• Most patients are male and nonsmokers.<br>• Almost all have chronic sinusitis<br>• Chest X-ray & HRCT show diffuse small centrilobular nodular opacities & hyperinflation |

These features tend to be characteristic of the respective diseases, but are not mandatory. For example,
a person who has never smoked may develop COPD (especially in the developing world where other risk factors may be more important than cigarette smoking) asthma may develop in adult and even in elderly patients.

## ► Treating Tobacco Use and Dependence:
### A clinical practice guideline- major findings & recommendations

- Tobacco dependence is a chronic condition that warrants repeated treatment until long-term or permanent abstinence is achieved.
- Effective treatments for tobacco dependence exist and all tobacco users should be offered these treatments.
- Clinicians and health care delivery systems must operationalize the consistent identification documentation and treatment of every tobacco user at every visit.
- Brief smoking cessation counselling is effective and every tobacco user should be offered such advice at every Contact with health Care providers.
- There is a strong dose-response relation between the intensity tobacco dependence counselling and its effectiveness.
- Three types of counselling have been found to be especially effective: practical counselling, social support of support arranged outside of treatment.
- First-line pharmacotherapies for tobacco dependence - varenicline bupropion sustained release, nicotine gum, nicotine inhaler, nicotine nasal spray, and nicotine patch-are effective and at least one of these medications should be prescribed in the absence of contraindications.
- Financial incentive programs for smoking cessation may facilitate smoking cessation.
- Tobacco dependence treatments are cost effective interventions.

## Smoking in pregnancy

Smoking **reduces birth weight** which may be of critical importance if the baby is born pre-term.

On average, the babies of smokers weigh 170 g less than non-smokers, but the **reduction in birth weight** is **related to the number of cigarettes** smoked **per day.**

Smoking is also associated with an increased risk of **miscarriage** and **still birth**. The infant has a greater risk of **sudden infant death syndrome**. There is some evidence that maternal smoking may adversely **affect ovarian function in female children.**

**No dysmorphic facies** syndrome has yet been described.
Maternal smoking has been shown to **increase lung maturity**, possibly by enhancing the production or secretion of cortisol. This makes neonates less likely to develop respiratory distress syndrome, but as lung maturation is often abnormal babies may have reduced lung function and increased rates of other respiratory illnesses.

**The Medical Research Council (MRC) dyspnea scale should be used to grade the breathlessness according to the level of exertion required to elicit it.**

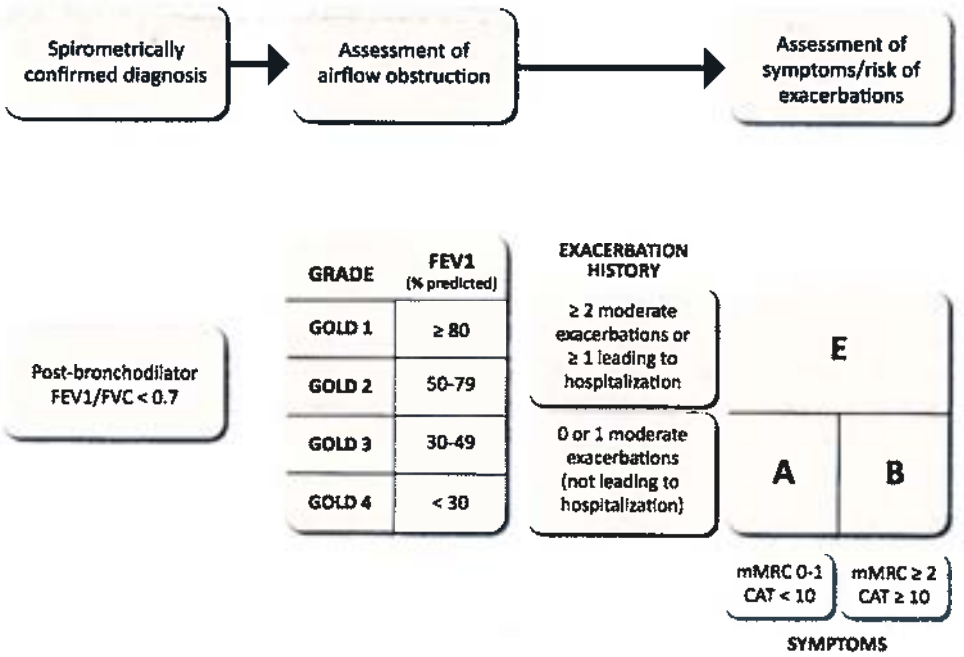
## MRC dyspnea scale Grade Degree of breathlessness related to activities:

- Not troubled by breathlessness except on strenuous exercise.
- Short of breath when hurrying or walking up a slight hill.
- Walks slower than contemporaries on level ground because of breathlessness, or has to stop for breath when walking at own pace.
- Stops for breath after walking about 100 meters or after a few minutes on level ground.
- Too breathless to leave the house, or breathless when dressing or undressing.

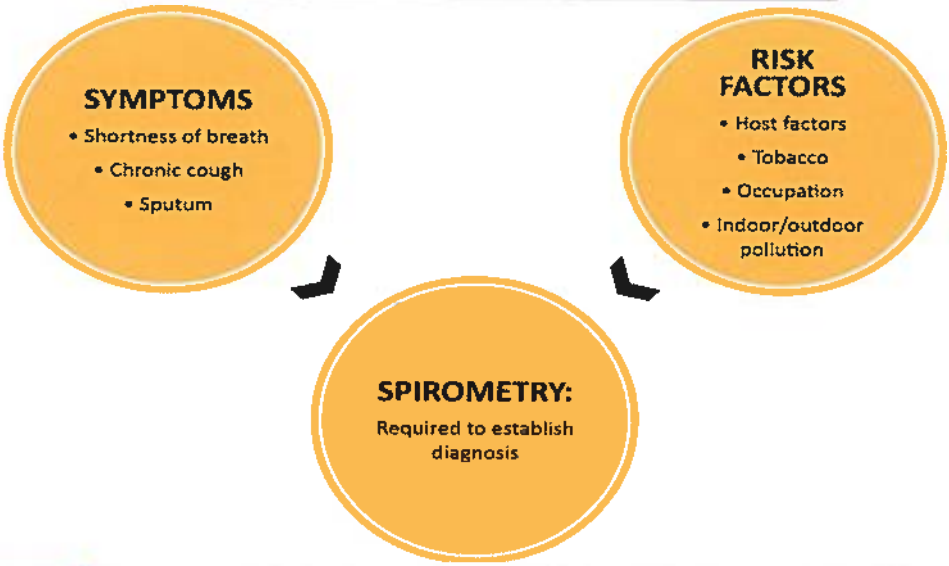
## The following investigations are recommended in patients with suspected COPD:

- Post-bronchodilator **spirometry** to demonstrate airflow obstruction: **FEV1/FVC ratio less than 70%,** with normal TLC (total lung capacity).
- **Chest x-ray:** hyperinflation, bullae, flat hemi-diaphragm. Also important to exclude lung cancer.
- **CBC:** exclude secondary polycythaemia and Body mass index **(BMI)** calculation.

## GOLD ABE Assessment Tool




## PATHWAYS TO THE DIAGNOSIS OF COPD



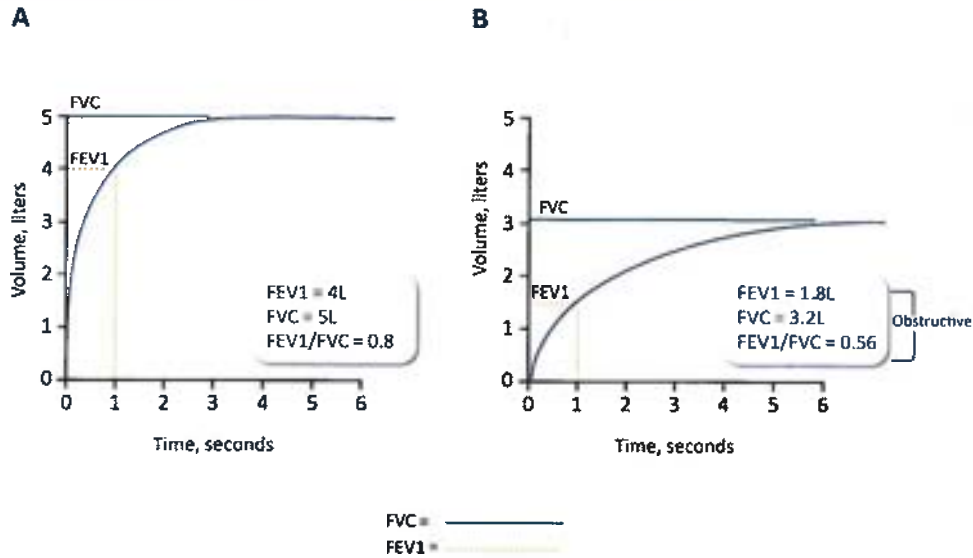
| ► GOLD Grades and Severity of Airflow Obstruction in COPD (based on post-bronchodilator $FEV_1$) | | |
|---|---|---|
| **In COPD patients (FEV1/FVC < 0.7):** | | |
| **GOLD 1:** | Mild | $FEV_1 \geq 80\%$ predicted |
| **GOLD 2:** | Moderate | $50\% \leq FEV_1 < 80\%$ predicted |
| **GOLD 3:** | Severe | $30\% \leq FEV_1 < 50\%$ predicted |
| **GOLD 4:** | Very Severe | $FEV_1 < 30\%$ predicted |

- **FEV1** is used for assessment of **severity** of COPD, **NOT FOR DIAGNOSIS.**
- Measuring peak expiratory flow **(PEFR)** is of **limited value in COPD**, as it may underestimate the degree of airflow obstruction.
- Note that if the FEV1 is greater than 80% predicted but the post-bronchodilator FEV1/FVC is < 0.7 >>> it is classified as Stage 1 (mild).
- Patients can now be diagnosed with **'mild' COPD** if their **FEV1 predicted is > 80%** if they have **symptoms suggestive of COPD.**
- Symptoms should be present to diagnose COPD in these patients.
- The pathology is centrilobular or panacinar with **loss of elastic tissue recoil**.

## Considerations in Performing Spirometry

| | |
|---|---|
| **PREPARATION** | • Spirometers should produce hard copy or have a digital display of the expiratory curve to permit detection of technical errors or have an automatic prompt to identify an unsatisfactory test and the reason for it<br>• The supervisor of the test needs training in optimal technique and quality performance<br>• Maximal patient effort in performing the test is required to avoid underestimation of values and hence errors in diagnosis and management |
| **PERFORMANCE** | • Spirometry should be performed following national and/or international recommendations*<br>• The expiratory volume/time traces should be smooth and free from irregularities<br>• The pause between inspiration and expiration should be < one second<br>• The recording should go on long enough for a volume plateau to be reached, which may take more than 15 seconds in severe disease<br>• Both FVC and FEV1 should be the largest value obtained from any of three technically satisfactory curves and the FVC and FEV1 values in these three curves should vary by no more than 5% or 150 mL, whichever is greater<br>• The FEV1/FVC ratio should be taken from the technically acceptable curve with the largest sum of FVC and FEV1 |
| **BRONCHODILATION** | • Possible dosage protocols are 400 mcg short-acting beta$_2$-agonist, 160 mcg short-acting anticholinergic, or the two combined*; FEV1 should be measured 10-15 minutes after a short-acting beta$_2$-agonist is given, or 30-45 minutes after a short-acting anticholinergic or a combination of both classes of drugs<br>• Patients already on bronchodilator treatment, in whom spirometry is requested for monitoring purposes do not need to stop their regular treatment for spirometry |
| **EVALUATION** | • Spirometry measurements are evaluated by comparison of the results with appropriate reference values based on age, height, sex, and race<br>• The presence of a postbronchodilator FEV1/FVC < 0.7 confirms the presence of non-fully reversible airflow obstruction |

A. Spirometry - Normal Trace B. Spirometry - Airflow Obstruction
Figure 2.1




## COPD: management of acute exacerbations

The most common bacterial organisms that cause infective exacerbations of COPD are:

- **Haemophilus influenzae** (most common cause)
- Streptococcus pneumoniae
- Moraxella catarrhalis
- Respiratory viruses account for around 30% of exacerbations, with the human **rhinovirus** being the most important pathogen
- Increase frequency of **bronchodilator** use and consider giving via a **nebuliser.**
- Give **prednisolone 30 mg daily for 7-14 days**. Prolonged courses offer no additional benefit.
- It is common practice for all patients with an exacerbation of COPD to receive **antibiotics.** NICE do not support this approach. They recommend giving oral antibiotics 'if sputum is purulent or there are clinical signs of pneumonia'.
- **NIV** should therefore be considered within the first 60 minutes of hospital arrival in all patients with an acute exacerbation of COPD in whom a respiratory acidosis persists despite maximal medical therapy (controlled O2, nebulised salbutamol and ipratropium, prednisolone, antibiotic (where indicated).

## ► Key Points for The Management of Exacerbations

- Short-acting inhaled beta-agonists, with or without short-acting anticholinergics, are recommended as the initial bronchodilators to treat an acute exacerbation (Evidence C)
- Systemic corticosteroids can improve lung function ($FEV_1$), oxygenation and shorten recovery time and hospitalization duration. Duration of therapy should not be more than 5-7 days (Evidence A)
- Antibiotics, when indicated, can shorten recovery time, reduce the risk of early relapse treatment failure, and hospitalization duration. Duration of therapy should be 5-7 days (Evidence B)
- Methylxanthines are not recommended due to increased side effect profiles (Evidence B)
- Non-invasive mechanical ventilation should be the first mode of ventilation used in COPD patients with acute respiratory failure who have no absolute contraindication because it improves gas exchange, reduces work of breathing and the need for intubation decreases hospitalization duration and improves survival **(Evidence A).**

- ➢ Pneumonia >>>>>>> **Strept. Pneumonia**
- ➢ Infective exacerbation of COPD >>>>>> **H. influenzae**

**EX**: Pt has COPD with palpitation with MAT >>> Stop Ventolin, low flow O2, Verapamil 5 mg IV then orally 40-120 mg/day TDS

## ► Differential Diagnosis of COPD Exacerbation

when there is clinical suspicion of the following acute conditions, consider the following investigations:

- **PNEUMONIA**
  - ➢ Chest radiograph
  - ➢ Assessment of C-reactive protein (CRP) and/or procalcitonin
- **PNEUMOTHORAX**
  - ➢ Chest radiograph or ultrasound
- **PLEURAL EFFUSION**
  - ➢ Chest radiograph or ultrasound
- **PULMONARY EMBOLISM**
  - ➢ D-dimer and/or Doppler sonogram of lower extremities
  - ➢ Chest tomography - pulmonary embolism protocol
- **PULMONARY EDEMA DUE TO CARDIAC RELATED CONDITIONS**
  - ➢ Electrocardiogram and cardiac ultrasound
  - ➢ Cardiac enzymes
- **CARDIAC ARRHYTHMIAS-ATRIAL FIBRILLATION/FLUTTER**
  - ➢ Electrocardiogram

## Key Points for The Management of Patients With COPD And Suspected Or Proven COVID-19

### SARS-CoV-2 Testing

- Swab/Saliva PCR if new or worsening respiratory symptoms, fever, and/or any other symptoms that could be COVID related

### Other Investigations

- Avoid spirometry unless essential
- Consider CT for COVID pneumonia and to exclude other diagnoses e.g. PE
- Avoid bronchoscopy unless essential
- Assess for co-infection

### COPD Pharmacotherapy

- Ensure adequate supplies of medication
- Continue maintenance therapy unchanged including ICS
- Use antibiotics and oral steroids in line with recommendations for exacerbations
- Avoid nebulization when possible

### COPD Non-Pharmacological Therapy

- Maintain physical activity as able

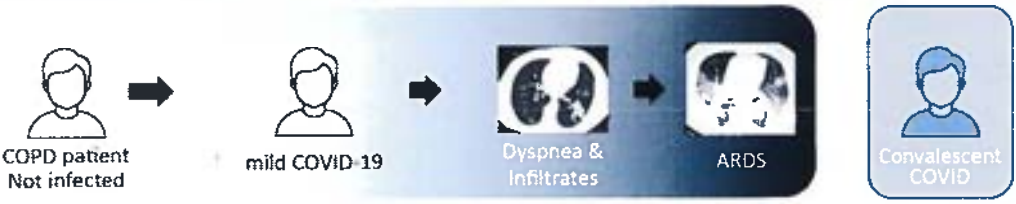
### Protective Strategies

- Have the COVID-19 vaccination in line with national recommendations.
- Follow basic infection control measures
- Maintain physical distancing
- Wear a face covering

### COVID-19 Therapy

- Use systemic steroids and remdesivir as recommended for patients with COVID-19
- Use HFNT or NIV for respiratory failure if possible .
- Use invasive mechanical ventilation if HFNT or NIV fails
- Post COVID-19 rehabilitation
- Ensure appropriate post COVID-19 follow-up

## ▶ COVID-19 & COPD




| | | | | | |
|---|---|---|---|---|---|
| **Clinical Features** | **COPD:** Cough, SOB | Mild constitutional symptoms Fever >37.5 °C, ↑SOB Dry Cough, Fatigue, Diarrhea | ↑↑ SOB± thypoxia $PaO_2/FiO_2 \leq 300$ mmHg | ARDS SIRS/Shock Cardiac Failure VTE | Fatigue SOB Cough |
| **Abnormal Investigations** | | SARS-CoV-2 PCR CXR/CT, $SpO_2$ Lymphopenia Thrombocytopenia CRP, D-dimer | CXR/CT, $SpO_2$ Lymphopenia Thrombocytopenia Transaminases D-dimer, PCT | $SpO_2$ CRP, LDH, IL-6 D-dimer, ferritin troponin, BNP | PFT CT Chest |
| **Continue Usual COPD Maintenance Therapy** | | | | | |
| **Possible Interventions** | Home Exercise Protective Strategies | Protective Strategies, COPD Exacerbation Therapy Low intensity exercise Therapeutic Trials | Controlled Oxygen Systemic Steroids Remdesivir Anticoagulation Therapeutic Trials | NIV, HFNT IMV Prone positioning Anticoagulation Therapeutic Trials | Home Exercise PR |

(ARDS, Adult respiratory distress syndrome; BNP, brain natriuretic peptide; CRP, C reactive protein; CT, computed tomography: CXR, chest radiograph; HFNT, high fow nasal aterapy, IL-6, interleukin 6; IMV, invasive mechanical ventilation; LDH, lactate dehydrogenase NIV non-invasive ventilaton PCT procalcitonin; PFT pulmonary function tests; PR. pulmonary rehablitation; SOB, Shortness of breath; $SpO_2$, peripheral oxygen saturation VTE, venous thromboembolism)

## COPD:

Management of stable patient Last updated 26 July 2019 by NICE and GOLD 2023

### General management:

- **Smoking cessation advice**
- Annual **influenza** vaccination
- One-off **pneumococcal** vaccination every 5 years.

### Inhalation therapy:

**Short-acting beta2 agonists (SABA) and short-acting muscarinic antagonists (SAMA):**

Use short-acting bronchodilators, as necessary, as the initial empirical treatment to relieve breathlessness and exercise limitation.

**Inhaled corticosteroids (ICS):**

- Do not use oral corticosteroid reversibility tests to identify which people should be prescribed inhaled corticosteroids, because they do not predict response to inhaled corticosteroid therapy. Be aware of, and be prepared to discuss with the person, the risk of side effects (including pneumonia) in people who take inhaled corticosteroids for COPD.

**long-acting beta2 agonists (LABA), and inhaled corticosteroids (ICS):**

- Do not assess the effectiveness of bronchodilator therapy using lung function alone. Include a variety of other measures such as improvement in symptoms, activities of daily living, exercise capacity, and rapidity of symptom relief.

**Consider LABA+ICS for people who:**

- have spirometrically confirmed COPD

**AND**

- have asthmatic features/features suggesting steroid responsiveness

**AND**

- remain breathless or have exacerbations despite: — having used or been offered treatment for tobacco dependence if they smoke and — optimised non-pharmacological management and relevant vaccinations and — using a short-acting bronchodilator

**Offer LAMA+LABA to people who:**

- have spirometrically confirmed COPD and
- do not have asthmatic features/features suggesting steroid responsiveness and
- remain breathless or have exacerbations despite: — having used or been offered treatment for tobacco dependence if they smoke and — optimised non-pharmacological management and relevant vaccinations and — using a short-acting bronchodilator.

**Before starting LAMA+LABA+ICS, conduct a clinical review to ensure that:**

- the person's non-pharmacological COPD management is optimised and they have used or been offered treatment for tobacco dependence if they smoke
- acute episodes of worsening symptoms are caused by COPD exacerbations and not by another physical or mental health condition
- the person's day-to-day symptoms that are adversely impacting their quality of life are caused by COPD and not by another physical or mental health condition.

**For people with COPD who are taking LABA+ICS, offer LAMA+LABA+ICS if:**

- their day-to-day symptoms continue to adversely impact their quality of life or
- they have a severe exacerbation (requiring hospitalization) or
- they have 2 moderate exacerbations within a year.

**For people with COPD who are taking LAMA+LABA, consider LAMA+LABA+ICS if:**

- they have a severe exacerbation (requiring hospitalisation) or
- they have 2 moderate exacerbations within a year.

**For people with COPD who are taking LAMA+LABA and whose day-to-day symptoms adversely impact their quality of life:**

- consider a trial of LAMA+LABA+ICS, lasting for 3 months only
- after 3 months, conduct a clinical review to establish whether or not LAMA+LABA+ICS has improved their symptoms: — if symptoms have not improved, stop LAMA+LABA+ICS and switch back to LAMA+LABA — if symptoms have improved, continue with LAMA+LABA+ICS.

## BRONCHODILATORS IN STABLE COPD

- Inhaled bronchodilators in COPD are central to symptom management and commonly given on a regular basis to prevent or reduce symptoms **(Evidence A)**
- Regular and as-needed use of SABA or SAMA improves FEV, and symptoms **(Evidence A).**
- Combinations of SABA and SAMA are superior compared to either medication alone in improving FEV, and symptoms **(Evidence A).**
- LABAs and LAMAs significantly improve lung function, dyspnea, health status, and reduce exacerbation rates **(Evidence A)**
- LAMAs have a greater effect on exacerbation reduction compared with LABAs (Evidence A) and decrease hospitalizations **(Evidence B)**
- Combination treatment with a LABA and LAMA increases FEV and reduces symptoms compared to monotherapy **(Evidence A)**
- Combination treatment with a LABA/LAMA reduces exacerbations compared to monotherapy **(Evidence B)**
- Tiotropium improves the effectiveness of pulmonary.rehabilitation in increasing exercise performance **(Evidence B).**
- Theophylline exerts a small bronchodilator effect in stable COPD **(Evidence A)** and that is associated with modest symptomatic benefits **(Evidence B).**

## Summary of the recommendations from GOLD 2023

# Anti-Inflammatory Therapy In Stable COPD

### Inhaled Corticosteroids

- An ICS combined with a LABA is more effective than the individual components in improving lung function and health status and reducing exacerbations in patients with exacerbations and moderate to very severe COPD **(Evidence A)**
- Regular treatment with ICS increases the risk of pneumonia especially in those with severe disease **(Evidence A)**
- Lower blood and sputum eosinophils are associated with greater presence of proteobacteria, notably Haemophilus, increased bacterial infections & pneumonia
- Independent of ICS use, there is evidence that a blood eosinophil count < 2% increases the risk of pneumonia **(Evidences C)**
- Triple inhaled therapy of LABA+LAMA+ICS improves lung function, symptoms and health status, and reduces exacerbations, compared to LABA+ICS, LABA+LAMA or LAMA monotherapy **(Evidence A)** Recent data suggest a beneficial effect versus fixed-dose LABA+LAMA combinations on mortality in symptomatic COPD patients with a history of frequent and/or severe exacerbations.
- Single inhaler therapy may be more convenient and effective than multiple inhalers

### Oral Glucocorticoids

- Long-term use of oral glucocorticoids has numerous side effects **(Evidence A)** with no evidence of benefits **(Evidence C)**

### PDE4 Inhibitors

- In patients with chronic bronchitis, severe to very severe COPD and a history of exacerbations:
  - A PDE4 inhibitor improves lung function and reduces moderate and severe exacerbations **(Evidence A)**.
  - A PDE4 inhibitor improves lung function and decreases exacerbations in patients who are on fixed-dose LABA+ICS combinations **(Evidence A)**

### Antibiotics

- Long-term azithromycin and erythromycin therapy reduces exacerbations over one year **(Evidence A).**
- Treatment with azithromycin is assaciated with an increased incidence of bacterial resistance **(Evidence A)** and hearing test impairments **(Evidence B)**

### Mucoregulators And Antioxidant Agents

- Regular treatment with mucolytics such as erdosteine, carbocysteine and NAC reduces the risk of exacerbations in select populations **(Evidence B)**

### Other Anti-Inflammatory Agents

- Simvastatin does not prevent exacerbations in COPD patients at increased risk of exacerbations and without indications for statin therapy **(Evidence A).** However, observational studies suggest that statins may have positive effects on some outcomes in patients with COPD who receive them for cardiovascular and metabolic indications **(Evidence C).**
- Leukotriene modifiers have not been tested adequately in COPD patients.

## Some more details

## Oral therapy:

### Oral corticosteroids:

- Long-term use of oral corticosteroid therapy in COPD is not normally recommended. Some people with advanced COPD may need long-term oral corticosteroids when these cannot be withdrawn following an exacerbation. In these cases, the dose of oral corticosteroids should be kept as low as possible.
- Monitor people who are having long-term oral corticosteroid therapy for osteoporosis, and give them appropriate prophylaxis. Start prophylaxis without monitoring for people over 65.

### Oral theophylline:

- The term theophylline refers to slow-release formulations of the drug. Theophylline should only be used after a trial of short-acting bronchodilators and long-acting bronchodilators, or for people who are unable to use inhaled therapy, as plasma levels and interactions need to be monitored

### Oral mucolytic therapy:

- Consider mucolytic drug therapy for people with a chronic cough productive of sputum. Only continue mucolytic therapy if there is symptomatic improvement (for example, reduction in frequency of cough and sputum production).
- Do not routinely use mucolytic drugs to prevent exacerbations in people with stable COPD.

### Oral anti-oxidant therapy:

- Treatment with alpha-tocopherol and beta-carotene supplements, alone or in combination, is not recommended.

### Oral anti-tussive therapy:

- Anti-tussive therapy should not be used in the management of stable COPD.

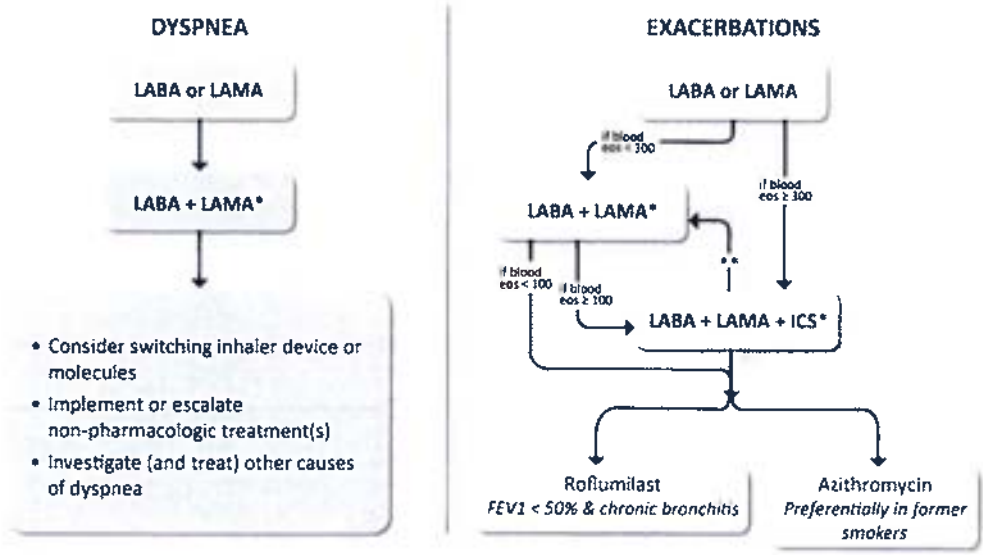
### Oral prophylactic antibiotic therapy:

- Before starting prophylactic antibiotic therapy in a person with COPD, think about whether respiratory specialist input is needed. Consider azithromycin (usually 250 mg 3 times a weekly.

## Summary of Treatment Recommendations GOLD 2023

# Follow-up Pharmacological Treatment

1. **IF RESPONSE TO INITIAL TREATMENT IS APPROPRIATE, MAINTAIN IT.**
2. IF NOT:
   - Check adherence, inhaler technique and possible interfering comorbidities
   - Consider the predominant treatable trait to target (dyspnea or exacerbations)
     - Use exacerbation pathway if both exacerbations and dyspnea need to be targeted
   - Place patient in box corresponding to current treatment & follow indications
   - Assess response, adjust and review
   - These recommendations do not depend on the ABE assessment at diagnosis




*Single inhaler therapy may be more convenient and effective than multiple inhalers

**Consider de-escalation of ICS if pneumonia or other considerable side effects. In case of blood eos ≥ 300 cells/µl de-escalation is more likely to be associated with the development of exacerbations

## ► INTERVENTIONAL THERAPY IN STABLE COPD

### LUNG VOLUME REDUCTION SURGERY

- Lung volume reduction surgery improves survival in severe emphysema patients with an upper-lobe emphysema and low post-rehabilitation exercise capacity **(Evidence A)**

### BULLECTOMY

- In selected patients, bullectomy is associated with decreased dyspnea, improved lung function and exercise tolerance **(Evidence C)**.

### TRANSPLANTATION

- In appropriately selected patients with very severe COPD, lung transplantation has been shown to improve quality of life and functional capacity **(Evidence C)**

### BRONCHOSCOPIC INTERVENTIONS

- In select patients with advanced emphysema, bronchoscopic interventhons reduce end-expiratory lung volume and improve exercise tolerance, health status and lung function at 6-12 months following treatment. Endobronchial valves **(Evidence A)**; Lung coils (Evidence B); Vapor ablation **(Evidence B)**.

**Cor pulmonale:**

- Features include peripheral oedema, ↑JVP, systolic parasternal heave, loud P2.
- Use a **loop diuretic** for oedema.
- Consider long-term oxygen therapy (**LTOT**).
- ACEIs, CCBs and alpha blockers are not recommended by NICE.

# COPD: Long-Term Oxygen Therapy (LTOT)

The 2018 NICE guidelines on COPD and GOLD 2023 clearly define which patients should be assessed for and offered long-term oxygen therapy (LTOT). Patients who receive LTOT should breathe supplementary oxygen for **at least 15 hours a day.** **Oxygen concentrators** are used to provide a fixed supply for LTOT.

Assess patients if any of the following:

- Very severe airflow obstruction **(FEV1 < 30% predicted).** Assessment should be 'considered' for patients with severe airflow obstruction **(FEV1 30-49% predicted).**
- **Cyanosis**
- **Polycythaemia**
- **Peripheral oedema**
- **Raised jugular venous pressure**
- **Oxygen saturations** less than or equal to **92% on room air**

**LTOT should be offered to COPD patients with:**

**A PO2 of < 7.3 kPa (55 mmHg)**

**OR those with PO2 of 7.3 - 8 kPa (60 mmHg) and ONE of the following:**

- **Secondary polycythaemia**
- **Pulmonary hypertension**
- **Nocturnal hypoxemia**
- **Peripheral oedema** (Cor-pulmonale)

COPD >> LTOT>>>>>>>> if **2** measurements of **PO2 < 7.3 kPa at least 3 weeks apart**, and

**ABG** should be performed in a **stable state and free from exacerbation**, which should be at **least 4 weeks after** an exacerbation of the disease.

Adequate data for **LTOT** prolonging **survival** exist **only for** COPD although in practice it is assumed to apply in other chronic hypoxemic lung conditions.

**NICE guidance does not allow home O2 therapy (LTOT) based on PH, PCO2, FEV1 or exacerbation criteria.**

## Benefits of LTOT:

- ↓ Secondary polycythaemia.
- ↓ Sympathetic outflow.
- ↓ Salt and water retention.
- ↓ Cardiac arrhythmia.
- Improve sleep quality due to reduced hypoxia-induced sleep arousals

## SUMMARY OF RECOMMENDATIONS: FROM GOLD 2023

### Prescription OF Supplemental Oxygen to COPD Patients

**Arterial hypoxemia defined as:**

$PaO_2$ < 55 mmHg (7.3 kPa) or $SaO_2$ < 88%

or

$PaO_2$ > 55 but < 60 mmHg (> 7.3 kPa but < 8 kPa)
with right heart failure or erythrocytosis

↓

Prescribe supplemental orygen
and titrate to keep $SaO_2 \geq 90\%$

↓

**Recheck in 60 to 90 days to assess:**

- if supplemental oxycen is still indicated
- If prescribed supplemental oxycen is effective

## Smoking cessation

NICE released guidance in 2008 on the management of smoking cessation.

### General points include:

- patients should be offered nicotine replacement therapy (NRT), varenicline or bupropion - NICE state that clinicians should not favour one medication over another
- NRT, varenicline or bupropion should normally be prescribed as part of a commitment to stop smoking on or before a particular date (target stop date)
- prescription of NRT, varenicline or bupropion should be sufficient to last only until 2 weeks after the target stop date. Normally, this will be after 2 weeks of NRT therapy, and 3-4 weeks for varenicline and bupropion, to allow for the different methods of administration and mode of action.
- Further prescriptions should be given only to people who have demonstrated that their quit attempt is continuing
- if unsuccessful using NRT, varenicline or bupropion, do not offer a repeat prescription within 6 months unless special circumstances have intervened
- do not offer NRT, varenicline or bupropion in any combination

## Nicotine replacement therapy

- adverse effects include nausea & vomiting, headaches and flu-like symptoms
- NICE recommend offering a combination of nicotine patches and another form of NRT (such as gum, inhalator, lozenge or nasal spray) to people who show a high level of dependence on nicotine or who have found single forms of NRT inadequate in the past

## Varenicline

- a nicotinic receptor partial agonist
- should be started 1 week before the patients target date to stop
- the recommended course of treatment is 12 weeks (but patients should be monitored regularly and treatment only continued if not smoking)
- has been shown in studies to be more effective than bupropion
- nausea is the most common adverse effect.
- Other common problems include headache, insomnia, abnormal dreams
- varenicline should be used with caution in patients with a history of depression or self-harm.
- There are ongoing studies looking at the risk of suicidal behaviour in patients taking varenicline
- contraindicated in pregnancy and breast feeding

## Bupropion

- a norepinephrine and dopamine reuptake inhibitor, and nicotinic antagonist
- should be started 1 to 2 weeks before the patients target date to stop
- **small risk of seizures (1 in 1,000)**
- contraindicated in epilepsy, pregnancy and breast feeding. Having an eating disorder is a relative contraindication

## Pregnant women

NICE recommended in 2010 that all pregnant women should be tested for smoking using carbon monoxide detectors, partly because *'some women find it difficult to say that they smoke because the pressure not to smoke during pregnancy is so intense.'*. All women who smoke, or have stopped smoking within the last 2 weeks, or those with a CO reading of 7 ppm or above should be referred to NHS Stop Smoking Services.

## Interventions

- the first-line interventions in pregnancy should be cognitive behaviour therapy, motivational interviewing or structured self-help and support from NHS Stop Smoking Services
- the evidence for the use of NRT in pregnancy is mixed but it is often used if the above measures failure. There is no evidence that it affects the child's birthweight. Pregnant women should remove the patches before going to bed
- as mentioned above, varenicline and bupropion are contraindicated

## Alpha-1 antitrypsin deficiency (A1AT)

Alpha-1 antitrypsin (A1AT) deficiency is a common inherited condition caused by a **lack of a protease inhibitor (Pi)** normally produced by the **liver**.
The role of A1AT is to protect cells from enzymes such as neutrophil elastase.

### Genetics:

- Located on chromosome **14**
- Inherited in an **autosomal recessive / autosomal co-dominant fashion** (trusted sources are split on which is a more accurate description).
- Alleles classified by their electrophoretic mobility:

  (**M** for normal, **S** for slow, and **Z** for very slow)
- Normal = **PiMM**
- Homozygous **PiSS** (**60%** normal A1AT levels)
- Homozygous **PiZZ** (**10%** normal A1AT levels)

The genotype **PiZZ** is associated with the **most severe form** of alpha 1-antitrypsin deficiency as the circulating levels of A1AT are 10-15% of normal.

Cigarette smoking is especially harmful to those with A1AT deficiency and can accelerate the progression of emphysema by 10 years.

**The serum levels of some of the common genotypes are:**

- **PiMM**: **100%** (normal)
- PiMS: 80% of normal serum level of A1AT
- **PiSS**: **60%** of normal serum level of A1AT
- PiMZ: 60% of normal serum level of A1AT
- PiSZ: 40% of normal serum level of A1AT
- **PiZZ**: **10-15%** (severe alpha 1-antitrypsin deficiency).

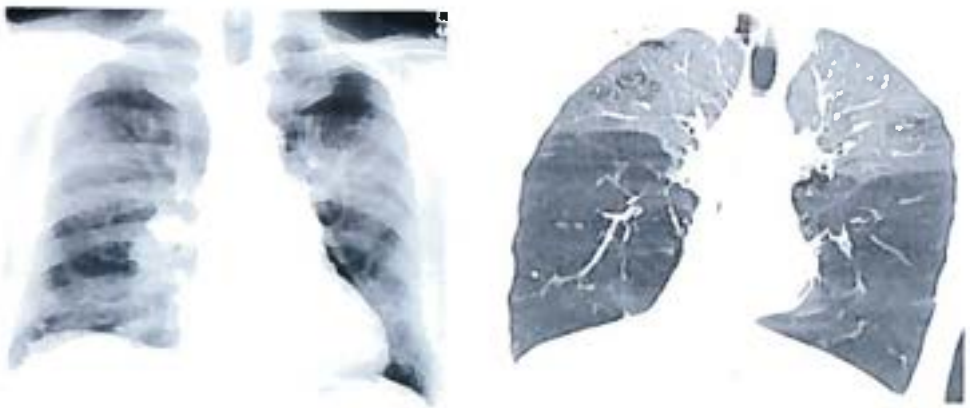
**NB:** Heterozygote patients such as those with the PiMZ genotype have alpha-1 antitrypsin levels approximately 35% of normal. They therefore have a low risk of developing clinically evident lung disease.

A1AT deficiency is an autosomal co-dominant disorder - both alleles contribute to the phenotype. The most common allele is **M (normal)**, whilst there are **over 100 abnormal alleles** (leading to decreased A1AT levels) the most common are Z and S.

Individuals with a single normal allele may have reduced levels of A1AT but still produce sufficient normal protein to prevent development of a disease phenotype, this is why some texts will refer to the condition as **autosomal recessive**.

## Features:

- Patients who manifest disease usually have **PiZZ** genotype
- Lungs: panacinar emphysema, most marked in lower lobes



CT of the chest and x-ray in the same 30-year-old woman with $\alpha_1$-antitrypsin deficiency. Coronal reformation of the CT demonstrates extensive panlobular emphysema of the mid and lower lung zones, which is a typical distribution of this condition. The vascular markings are more prominent in the upper lobes, showing "cephalization" of flow.

- Liver: **cirrhosis** and **hepatocellular carcinoma** in adults, cholestasis in children.
- A1AT deficiency is associated with a number of **malignancies** including **hepatocellular** cancer, **lung** cancer, bladder cancer and **lymphoma**.
- Other associated conditions include
  - Pancreatitis
  - Gall stones
  - **Primary sclerosing cholangitis (PSC)**

- COPD
- Bronchiectasis
- Wegener's granulomatosis and
- Pelvic prolapse.

**Young** pt. with **COPD** + **non-smoker** + family history + **Liver** >>> **A1AT**.

## Investigations:

- **A1AT concentrations**
- spirometry: obstructive picture

## Management:

- No smoking
- Supportive: bronchodilators, physiotherapy
- IV recombinant alpha1-antitrypsin protein concentrates
- Surgery: volume reduction surgery, lung transplantation

# Oxygen therapy

**In patients who are critically ill (anaphylaxis, shock etc.) oxygen should initially be given via a reservoir mask at 15 l/min. Hypoxia kills.**

The BTS guidelines specifically exclude certain conditions where the patient is acutely unwell (e.g. myocardial infarction) but stable.

## Oxygen saturation targets:

- Acutely ill patients: 94-98%.
- Patients at risk of hypercapnia (e.g. COPD patients): 88-92%.
- Oxygen should be reduced in stable patients with satisfactory oxygen saturation.

Any Pt with **COPD** >>> **Contraindicated High** flow Oxygen.

Patient with acute exacerbation of COPD and suffering from hypoxia and hypercapnia >>> the **respiratory centre** was **solely stimulated by hypoxia**. That is why his respiratory effort will become less and the condition worsened when he was given **high concentration oxygen**, **depriving him of hypoxic drive.**

## O2 THERAPY IN COPD patients:

- Prior to availability of blood gases, use a 28% Venturi mask **at** 4 l/min and aim for an oxygen saturation of 88-92% for patients with risk factors for hypercapnia but no prior history of respiratory acidosis.
- Adjust target range to 94-98% if the pCO2 is normal.

**NB:** Target O2 Sat% in COPD:

- **88-92%** IF associated with **HIGH** PCO2 use ventory mask 28% at 4 l/min
- **94-98%** IF associated with **NORMAL** PCO2

**NB:** When managing patients with COPD, once the pCO2 is known to be normal the target oxygen saturations should be 94-98%.

**Situations where oxygen therapy should NOT be used routinely if there is no evidence of hypoxia:**

- Acute coronary syndromes (MI)
- Stroke
- Obstetric emergencies
- Anxiety-related hyperventilation

## Non-invasive ventilation (NIV)

NIV is the treatment of choice for **persistent hypercapnic** ventilation failure despite optimal medical therapy.

It has been shown in RCTs to reduce intubation rate and mortality in COPD patients with decompensated respiratory acidosis (pH <7.35 and $pCO_2$ >6 kPa).

NIV should therefore be considered **within the first 60 minutes** of hospital arrival in all patients with **an acute exacerbation of COPD** in whom a **respiratory acidosis persists** despite maximal medical therapy (controlled oxygen, nebulised salbutamol and ipratropium, prednisolone, antibiotic where indicated).

### Key indications:

- **COPD** with respiratory acidosis **pH 7.25-7.35.**
- **Type II** respiratory failure secondary to **chest wall deformity, neuromuscular** disease or **obstructive sleep apnoea**
- **Cardiogenic pulmonary oedema unresponsive** to CPAP
- **Weaning** from tracheal intubation

### Recommended initial settings for bi-level pressure support (bi-PAP) in COPD:

- Expiratory Positive Airway Pressure **(EPAP): 4-5 cm H2O**
- Inspiratory Positive Airway Pressure **(IPAP):** RCP advocate **10 cmH2O** whilst BTS suggest **12-15 cm H2O.** IPAP should be increased by 2-5 cm increments every 10 minutes, with a usual target of 20 $cmH_2O$ or until a therapeutic response is achieved.

- Back up **rate: 15 breaths/min**
- Back up inspiration: expiration ratio: **(I:E ratio 1:3)**
- **FiO2 not > 40%.**
- **Keep SpO2 88 - 92%**
- ABG every 1-2 hr. ABGs should be repeated after 1 hour of NIV therapy, and 1 hour after subsequent change in settings or 4 hours in stable patients.

If the **pH is < 7.25** >>>>> **invasive** ventilation should be considered.

A trial of **NIV** may be undertaken in **bronchiectasis** but should **not** be used routinely as its effectiveness is likely to be **limited** by **excessive secretions**

## Exceptions for NIV may be:

- **Haemodynamic instability** that is requiring **inotropes**.
- **Life threatening hypoxaemia** (when invasive ventilation may be more appropriate).
- Confusion / **impaired consciousness**
- Severe cognitive impairment (where NIV is not tolerated)
- Severe co-morbidity
- Facial burns/trauma/surgery
- Vomiting
- Fixed upper airway obstruction
- Undrained pneumothorax
- Upper GI surgery
- Unprotected airway,
- **Copious respiratory secretions**

## Hospital at home (HaH) treatment for COPD

A specific subtype of intermediate care is Hospital at Home (HaH), where active treatment is provided by healthcare professionals in the patient's home for a condition that otherwise would require hospital care.

BTS has issued recommendations as to whom HaH should be offered.

It recommends that HaH should **not** be offered in the below instances:

- Impaired level of consciousness.
- Acute confusion.
- PH <7.35, if ABG have been measured.
- Acute changes on chest radiograph.
- Concomitant medical problem requiring inpatient stay.

- Insufficient social support, no telephone, residence geographically remote from hospital.
- New hypoxaemia ($SpO_2$ 90%) - a contraindication if oxygen cannot be provided at home.

Although factors such as increasing age and duration of COPD have been shown in studies to identify those at increased risk of relapse, they have only a moderate sensitivity and specificity, and hence are not included in the listed contraindications.

Patient with **COPD** and want to travel by airport to japan. What would you advise him to **check his fitness to fly**?
A **hypoxic challenge test** gives the patient **FiO2 15%** for **15 minutes** and measures **PO2**:
- If **PaO2 > 7.4 kPa (> 55 mmHg) - Oxygen not required**.
- If PaO2 6.6-7.4 kPa (50-55 mmHg) - Borderline. A walk test may be helpful.
- If PaO2 < 6.6 kPa (< 50 mmHg) - In-flight oxygen (2L/min).

Also simply History, examination, assessment of severity of COPD and **$O_2$ sat at sea level** should be performed:
- Sea level **SpO2 > 95% - Oxygen not required**
- Sea level SpO2 92-95% and no risk factor - Oxygen not required
- Sea level SpO2 92-95% and additional risk factor - Perform hypoxic challenge test with arterial or capillary measurements
- Sea level SpO2 < 92% - In-flight oxygen
- Receiving supplemental oxygen at sea level - Increase the flow while at cruising altitude.

**NB**: COPD with infective exacerbation: usually develop **respiratory acidosis**, so check **HCO3** if still normal so this is **acute** respiratory acidosis and may need **(Bi-PAP) NIPPV** (non-invasive positive pressure ventilator), alternative include **Doxapram IVI**, a central respiratory stimulant, these would be combined with appropriate antimicrobial therapy. It should only be used **when Bi-PAP is unavailable** or in the case of **reduced respiratory drive due to** sedative or anaesthetic agents. Doxapram also has a number of contraindications, which include **HTN** (relative contraindications).

**EX**: **Spirometry and reversibility** is the investigation of choice in patients with asthma, smoker and farmer:
An **obstructive** defect **with** reversibility >>> **Asthma**
An **obstructive** defect **without** reversibility >>> **COPD**
A **restrictive** defect >>> would support a diagnosis of **farmer's** lung

# Bronchiectasis

Bronchiectasis describes a permanent dilatation of the airways secondary to chronic infection or inflammation. There are a wide variety of causes are listed below:

## Causes

- post-infective: tuberculosis, measles, pertussis, pneumonia
- cystic fibrosis
- bronchial obstruction e.g. lung cancer/foreign body
- immune deficiency: selective IgA, hypogammaglobulinaemia
- allergic bronchopulmonary aspergillosis (ABPA)
- ciliary dyskinetic syndromes: Kartagener's syndrome, Young's syndrome
- yellow nail syndrome

Chest X-ray and CT scan from a patient who presented with dyspnoea. The x-ray shows reitcular opacities predominantly in the bases. In addition the CT demonstrates honeycombing and traction bronchiectasis

Chest x-ray showing tramlines, most prominent in the left lower zone

CT chest showing widespread tram-track and signet ring signs

## Management

Bronchiectasis describes a permanent dilatation of the airways secondary to chronic infection or inflammation.

After assessing for treatable causes (e.g. immune deficiency) management is as follows:

- physical training (e.g. inspiratory muscle training) - has a good evidence base for patients with non-cystic fibrosis bronchiectasis
- postural drainage
- antibiotics for exacerbations + long-term rotating antibiotics in severe cases
- bronchodilators in selected cases
- immunisations
- surgery in selected cases (e.g. Localised disease)

### Most common organisms isolated from patients with bronchiectasis:

- Haemophilus influenzae (most common)
- Pseudomonas aeruginosa
- Klebsiella spp.
- Streptococcus pneumonia

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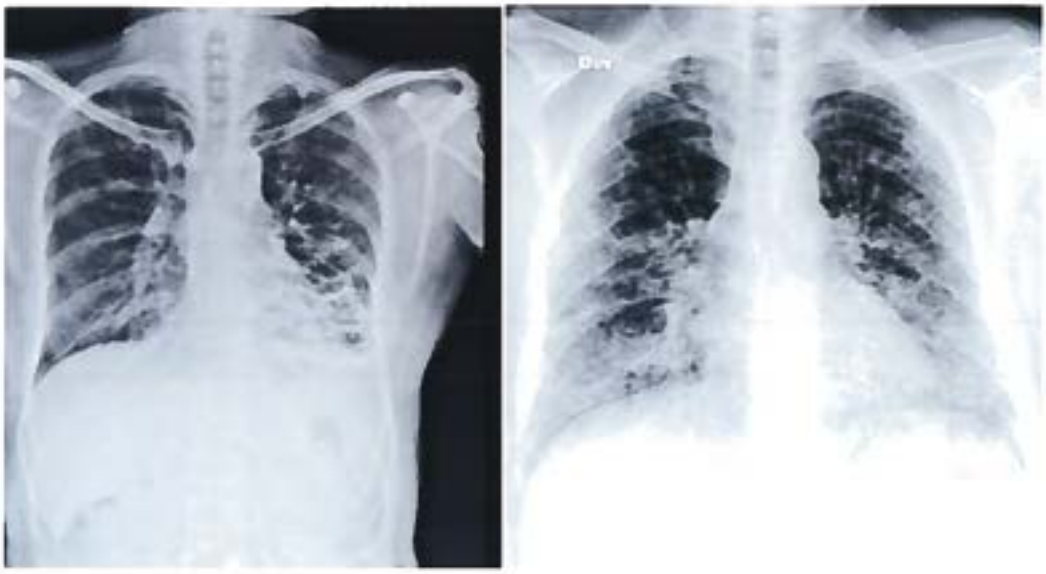

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## Kartagener's syndrome (Immotile cilia syndrome)

Kartagener's syndrome; also known as **primary ciliary dyskinesia (PCD)** and **immotile cilia syndrome** was first described in 1933 and most frequently occurs in examinations due to its association with dextrocardia in 50% of cases (e.g. 'quiet heart sounds', 'small volume complexes in lateral leads').
It is an inherited condition as an **autosomal recessive** disorder where the cilia lining the airways fail to function or function ineffectively due to a defect in the dynein molecule.

### Features:

- **Dextrocardia** (in **50%** of cases), or complete situs inversus totalis.
- **Bronchiectasis**
- **Recurrent sinusitis**
- **Subfertility** (secondary to diminished sperm motility and defective ciliary action in the fallopian tubes)

Other associated conditions of immotile cilia syndrome are: Congenital heart defects, Deafness and Hydrocephalus.

## Cystic fibrosis (CF syndrome)

### Basics:

- It is **autosomal recessive** disorder causing ↑ viscosity of secretions e.g. lungs and pancreas.
- It is due to **defect** in the cystic fibrosis transmembrane conductance regulator **(CFTR) gene,** which codes a **cAMP – regulated chloride channel** found in secretory epithelia.
- The airways become obstructed by thick mucus due to **defective chloride secretion** and **increased sodium resorption** across the airway epithelium.
- This leads to **bacterial colonisation** early in life with recurrent chest infection and bronchiectasis (**obstructive** lung disease by spirometry).
- The most common inherited lethal condition in **Caucasians.**
- In the UK 80% of CF cases are due to a deletion at delta F508 **(DF508 mutation)** on the **long arm of chromosome 7.**
- CF affects **1 per 2500** births, and the **carrier rate is 1 in 25.**
- Patients have **dry protein-rich secretions** which lead to complications of the pulmonary and gastrointestinal systems.

- CF is **the commonest cause of exocrine pancreatic insufficiency**.
- The disease presents with failure to thrive, steatorrhoea and abdominal pain. Diabetes mellitus can occur.

## Presenting features:

- Neonatal period (around 20%): **meconium ileus,** less commonly prolonged jaundice.
- Failure to thrive
- **Recurrent chest infections** (40%)
- **GIT: malabsorption (30%): steatorrhoea**, liver disease (10%), **cholesterol gall stones (10-30%)**, peptic ulcers, ↑ GI malignancy, **Constipation (dt defective CL secretion and ↑ Na absorption in the gut).**
- **Pan-opacification of the nasal sinuses** to be present in **all** CF patients

**Constipation** is common in patients with CF.

20 % have a fatty liver and gallstones are seen in 15% of young adults with the disease. Patients may also develop secondary biliary cirrhosis with mucus plugging of bile ducts and portal hypertension.

**Abdominal pain** with **cystic fibrosis** is due to **distal intestinal obstruction syndrome** (NOT by meconium ileus): occurs in 10-20% of patients with CF and incidence increases with age. About 80% of cases present for the first time in adults.

## Other features of cystic fibrosis:

- **Delayed development and puberty** (Almost **100%** of children)
- **Short stature**
- **Pancreatic insufficiency** is very common, **85%** of patients affected. So defective absorption of fat-soluble vitamins like AKED.
- **Diabetes Mellitus** (occurs in **>65%** of patients by age 25 and this is **independent** of weight gain).
- **Nasal polyps** 15-20% (most of these occurring in the 2nd decade).
- **Rectal prolapse** is usually **idiopathic,** occurring between 1 - 5 years (due to bulky stools). Following defecation the prolapse usually **resolves spontaneously**, or through manual reinsertion by the patient or parent.
- **Male infertility** (occurs in 98% of adult men, it is due to **mal-development of the vas deferens** or to other forms of **obstructive azoospermia).**
- **Female subfertility** (due to **viscid** cervical secretions).

Female patient with CF, **after treating the acute infection she has a good chance of a successful pregnancy.**

But observational studies suggest that patient with **FEV1 less than 60%** of that **predicted** have a much worse outcome both with respect to their own health status and the viability of the pregnancy, and that chronic pseudomonas infection and multiple exacerbations do much worse. ☹

## Organisms which may colonise CF pts.:

- It depends on the **age** of the patient:
  - Infants and young children become colonised by **Staphylococcus aureus** and then **Haemophilus influenzae**.
  - In teenagers, **Pseudomonas aeruginosa** colonisation occurs.
- **Pseudomonas** aeruginosa >>> **Treatment Inhaled Tobramycin**
- **Aspergillus**.
- **Burkholderia** cepacia. (previously called: Pseudomonas cepacia)
- Mycobacterium tuberculosis, other mycobacteria

Sputum samples should be obtained, and organism identification and sensitivities can be used to guide treatment of future exacerbations.

**EX**: A 17-year-old girl with known cystic fibrosis presents with a chest infection. What antibiotic would be most suitable for her >>> the usual combination is **ceftazidime** and **tobramycin**, for a period of **2 weeks**.

Gentamicin can be used in place of tobramycin, but has poorer pseudomonal cover and is associated with significant side effects (nephrotoxicity and ototoxicity).

**Cepacia Syndrome in CF:**

Rapidly progressive fever, ↑ volume of purulent sputum, uncontrolled bronchopneumonia, septicaemia, weight loss, and poor outcome.

Approximately 3% of CF patients are thought to be colonized with cepacia (Burkholderia cepacia).

**Treatment:**
* **Ceftazidime + Aminoglycosides**

## Diagnosis:

**Sweat test:** 2 reliable positive results on 2 separate days is diagnostic for CF. It is positive when **sweat chloride is more than > 60 mmol/L.**

The sweat test is conducted using **pilocarpine** iontophoresis.

A 3 mA current carries pilocarpine into the **skin of the forearm** stimulating local sweating. The arm is washed with distilled water and sweat collected on a filter paper or gauze. The **duration of collection is usually 30-60 minutes**. The filter paper is removed, weighed and eluted in distilled water.

**At least 50 mg and preferably 100 mg of sweat** should be collected for reliable results. It may not be possible to collect this amount in young infants.

**More than 60 mmol/L of chloride is diagnostic of CF** when one or more other criteria are present.

In healthy adults, the sweat chloride values increase slightly, but 60 mmol/L still differentiates CF from other conditions.

**False negative** results may be encountered in **nephrotic** syndromes.

Diagnosis of cystic fibrosis is usually clinical based on the **pulmonary** and **gastrointestinal** manifestations, family history and a positive sweat test. Confirmation is with genetic studies.

## Management of cystic fibrosis involves a multidisciplinary approach:

- Regular (at least twice daily) chest physiotherapy and postural drainage. Parents are usually taught to do this. Deep breathing exercises are also useful
- **High calorie** diet, including **high fat** intake ( this is now the standard recommendation - previously high calorie, low-fat diets have been recommended to reduce the amount of steatorrhoea)
- Vitamin supplementation as Vit. D
- **Pancreatic enzyme supplements** taken **with meals**, they are required to help patients maintain weight.
- **N-Acetylcysteine** can be used in moderate episodes. This loosens and softens the plugs, presumably by 'opening' the disulphide bonds in the abnormal intestinal mucus and maintains luminal patency. Also N-Acetylcysteine can be put down the NG tube in I.O.
- Heart and lung transplant
- Gene therapy remains the ultimate goal for treatment.
- **Human recombinant DNase** given as a **single daily aerosol** seems to improve pulmonary function, decrease the frequency of chest exacerbations, and promotes a sense of well-being in patients with mild to moderate disease with purulent secretions. This may be

because, in the inflamed airway, the nuclei from dead cells account for much of the viscidity of secretions.

Median survival has increased significantly over the past 10 years, and is now around **37 years** and is currently improving.

EX: A 25-year-old man who is known to have **DM** and suffers from **recurrent chest infections** is referred to the gastroenterology team with **chronic diarrhoea**. He has had **persistently abnormal liver function tests** over the last 3 months and an abdominal ultrasound scan showed a fatty liver and **gallstones.**

The most likely diagnosis is **Cystic fibrosis (CF)**

## Obstructive sleep apnoea/hypopnoea syndrome

It affects 1-2 % of the population and is most commonly found in **obese male smokers** with a background of **COPD**

### Predisposing factors:

- **Obesity**
- **Macroglossia: acromegaly, hypothyroidism, amyloidosis**
- **Large tonsils** and nasal deformities.
- **Marfan's syndrome**

Sleep apnoea causes include >> obesity and macroglossia

### Consequence:

- **Daytime somnolence:** The dominant symptom
- **Apnoea** many times per **night**, resulting in **reduction of REM sleep**
- **Hypertension**
- Impaired glucose tolerance (IGT), and **insulin resistance**.
- True nocturnal polyuria.
- **Cushing's** syndrome.
- It is an independent risk factor for **stroke** and **death.**

### Assessment of sleepiness:

- Epworth Sleepiness Scale (ESS) - questionnaire completed by patient +/- partner.
- Multiple Sleep Latency Test (MSLT) - measures the time to fall asleep in a dark room (using EEG criteria).

## Diagnostic tests:

- The diagnosis can usually be made by a **good history** from the sleeping partner, supported by **non-invasive oximetry** performed at home (**overnight home sleep oximetry**).
- **Polygraphic sleep studies (full polysomnographic studies):** ranging from monitoring of pulse oximetry at night to full polysomnography where a wide variety of physiological factors are measured including EEG, respiratory airflow, thoraco-abdominal movement, snoring and pulse oximetry.
- This full polysomnographic studies are rarely required for diagnosis but can be useful for research purposes.

## Management:

- **Weight loss.**
- **CPAP** is first line for moderate or severe OSAHS: dramatic effect.
- Intra-oral devices (e.g. mandibular advancement) may be used if CPAP is not tolerated or for patients with mild OSAHS where there is no daytime sleepiness.
- Limited evidence to support use of pharmacological agents.

# Pneumonia

**CURB-65 criteria** for evaluation of severe pneumonia:

- **C**onfusion (AMT = Abbreviated Mental Test score **≤ 8**/10)
- **U**rea > 7 mmol/L
- **R**espiratory rate ≥ 30 / min
- **B**P: systolic ≤ 90 or diastolic ≤ 60 mmHg
- Age ≥ **65** years

- Score of **0 or 1** are at low risk of death, and can be treated at **home** if the social circumstances are compatible.
- A score of **2** usually indicates **inpatient** treatment is required, but hospital-supervised outpatient treatment can be considered.
- Patients who have a CURB-65 score of **3 or more** are at high risk of death and have a **severe** pneumonia
- Those with scores of **4 and 5** should be for treatment in **ICU**.

**(CURB-65) and its associated mortality rates:**

- **Low** severity: CURB-65 **0-1**, mortality **<3%** **>>> Home ttt**
- **Moderate** severity: CURB-65 **2**, mortality **9% >>> Inpatient**
- **High** severity: CURB-65 **3-5**, mortality **15-40% >>> ICU**

A score of 0-1 is associated with a risk of mortality of **< 5%** from CAP.
A score of 2, the risk of mortality rise to be **13%**.
A score of 3, the risk of mortality rise to be **17%**.
A score of 4, the risk of mortality rise to be **42%**.
A score of 5, the risk of mortality rise to be **57%**

## Other less important factors associated with a poor prognosis include:

- Coexisting disease **(Comorbidity):** DM, IHD, CHF, CVS, Renal imp.
- **Hypoxemia** (SPO2 < 92%, PO2 < 8 kPa) regardless of FiO2.
- **Cyanosis.**
- **TLC:** <4000 or > 20,000 (**NOT Platelets** count).
- **Temperature** less than 35°C or more than 40°C.
- **CXR:** Multi-lobar infiltration
- Positive blood culture

## Community-acquired Pneumonia (CAP)

**Community acquired pneumonia (CAP) may be caused by the following infectious agents:**

- **Streptococcus pneumoniae** (accounts for around **80**% of cases)
- **Staphylococcus aureus**: **commonly after the 'flu,** ttt: Flucloxacillin or IV vancomycin.
- Haemophilus influenzae: is rare in patient age > 6 years, unless immunocompromised.
- Atypical pneumonias (e.g. due to Mycoplasma, legionella).
- Viruses.

**Streptococcus pneumoniae (pneumococcus)** is the most common cause of community-acquired pneumonia

**Characteristic features of pneumococcal pneumonia**

- Rapid onset
- High fever
- Pleuritic chest pain
- **Herpes labialis**

*Streptococcus pneumoniae* >>> reactivation of the HSV >>> 'cold sores'

CT scan of the patient demonstrating a confluent region of lung consolidation with ground-glass opacification on the margins of the consolidated lung commonly seen in bacterial pneumonia.

Posteroanterior CXR consolidation in the left lower lobe occupying all 3 basilar segments. There is blunting of the left costophrenic angle indicating a parapneumonic effusion.

## Management:

**Refer to NICE guidelines on management of hospital and community acquired pneumonia 2019.**

**CURB 0-1** (low severity) can be treated with **amoxicillin** 500 mg TDS PO.
**CURB 2** should be treated with **amoxicillin** 500 mg to 1 g TDS + **clarithromycin** 500 mg BID.
**CURB 3-5** (High severity) should be treated as soon as possible with: **co-amoxiclav** 1.2 g **IV** TDS + **clarithromycin** 500 mg **IV** BD.

- In the majority of patients CAP should be confirmed by **chest radiography before** the commencement of antibiotics.
- However, if patients are **critically unwell,** they should be treated for the presumptive diagnosis.
- Antibiotic treatment should be **initiated within 4 hours of presentation.**
- The **oral** route is recommended in those with low and moderate severity CAP.
- Patients treated with **parenteral** antibiotics initially should be **switched** to an **oral** regimen **once clinical improvement** is seen and the patients has been **afebrile for at least 24 hours**.
- For most patients with **uncomplicated** CAP **7 days** of antibiotic treatment is recommended.

For those with **high severity pneumonia** where an organism has not been identified, **7-10 days** treatment is indicated and extended to **14-21 days** where clinically needed.

- **Low or moderate severity CAP: oral amoxicillin+ macrolide** should be added for patients **admitted** to hospital
- **High severity CAP (CURB ≥ 3/5):**
  - **IV co-amoxiclav + IV clarithromycin**
  - OR cefuroxime + clarithromycin
  - OR cefotaxime + clarithromycin

**Staph aureus** >> treatment: **co**-prescription **Amoxicillin + Flucloxacillin (FLUMOX)**

Pneumonia in an **alcoholic – Klebsiella**

- **Klebsiella** pneumonia (**Friedlander's pneumonia**) typically occurs in middle-aged **alcoholic** men.
- CXR features may include **abscess** formation in the **upper/middle** lobes and empyema.
- The mortality rates are high approaches 30-**50%** regardless of treatment.

It is important for patients who had **pneumonia** and had a **consolidation** on chest x ray to have a **follow up chest x ray in 6 weeks** to ensure complete resolution. This is to exclude any underlying cause especially malignancy.

Note that: The most useful test to support your suspicious of diagnosis of empyema is >>> **Pleural PH less than 7.2**, it is **highly suggestive of empyema**.

**NB:** Pleural fluid microbiology and C&S are often not useful as organisms frequently do not grow.
**NB:** Pleural WBCs can be raised even in reactive pleural effusion.
**NB:** Pneumococcal antigen either in serum or urine could be negative and would not confirm whether the effusion is infected or reactive.

## Hospital-acquired pneumonia (HAP)

- **Within 5 days of admission**: co-amoxiclav or cefuroxime.
- **More than 5 days after admission**:
  - Piperacillin with tazobactam (e.g. **tazocin**).
  - OR a broad-spectrum cephalosporin (e.g. **ceftazidime**).
  - OR a quinolone (e.g. **ciprofloxacin**).

# Legionella Disease (LD)

- **Legionnaire's disease** is caused by the **intracellular** bacterium Legionella pneumophilia (Gm –ve bacilli).
- It occurs in 2-15% of community acquired pneumonia.
- It has an incubation period of 2-10 days.
- It is typically colonizes **water tanks** and hence questions may hint at **air-conditioning** systems, **showers** or **foreign holiday e.g. to Spanish.**
- Person-to-person transmission is not seen.
- Legionella is not sensitive to penicillin.
- Legionella resistance to rifampicin.

## Features:

- **Flu-like symptoms**
- **Dry** cough
- **Confusion**
- Relative bradycardia
- TLC may be high or low
- **Lymphopaenia, with marked leucocytosis.**
- **Hyponatraemia (dt SIADH)** >>>>fluid restriction
- **Deranged liver function tests** and **low ALP**
- 50% of cases have **GIT** symptoms: ANV, **Diarrhea,** Abd pain.
- CXR: Bilateral patchy consolidation ± pleural effusion (in up to 50%).
- Urine: **proteinuria, haematuria** and myoglobinuria.

## Diagnosis: **Urinary antigen test for legionella.**

It is the most useful test being rapidly available and accurate (70% specificity and 100% sensitivity).

The mortality rate may approach 100% in patients with underlying disease. In untreated patients, the mortality rate may be as high as 80%.

## Management:

- **Macrolides** are appropriate first line therapy e.g. **Clarithromycin** or Erythromycin.
- **Fluoroquinolones** and **doxycycline** are reasonable alternatives.
- Treatment of hyponatremia with legionnaire's >>> **Normal saline.**

It should be suspected in case of foreign travel or stay in hotels, failure to respond to penicillins, diarrhoea accompanying respiratory symptoms, deranged liver function tests and low sodium.

# Mycoplasma pneumoniae

- Mycoplasma pneumoniae is a cause of atypical pneumonia which often affects **younger** patients frequently among those living in boarding houses (housings, hostels).
- Epidemic pneumonia due to Mycoplasma infection is seen occasionally, example as **class mates have recently been ill.**
- **Epidemics** of Mycoplasma pneumoniae classically occur every 4 years.
- It is associated with a number of **characteristic complications** such as **erythema multiforme (target lesion)** and **cold autoimmune haemolytic anaemia due to presence of anti-I antibody.**
- It is important to recognise atypical pneumonias as they may **not respond** to penicillins or cephalosporins due to it lacking a peptidoglycan cell wall **(NO cell wall).**

## Features:

- The disease typically has a **prolonged** and slow onset of symptoms
- **Flu-like symptoms** classically precede **a dry cough**
- **Bilateral consolidation on CXR**
- The CXR findings are much worse than the clinical findings.
- Complications may occur as below

**Complications** (Extra-pulmonary manifestations): in up to 10% of cases:

- **Hematology**: **Cold agglutinins (IgM antibodies)** (In **50%** of cases) (which is **directed** against the I antigen of the erythrocyte membrane) and may cause a **haemolytic anaemia (↓Hb, fragmented RBCs, ↑RTX, ↑ bilirubin), thrombocytopenia.**
- **Skin: Erythema multiforme, erythema nodosum.**
- **Bullous myringitis:** painful vesicles on the tympanic membrane with erythematous ear ± occipital lymphadenopathy.
- **Neuro**: **Meningoencephalitis, Guillain-Barre syndrome**, Transverse myelitis, Cerebellar ataxia.
- **Heart**: **Pericarditis/myocarditis**
- **GIT**: **hepatitis, pancreatitis**
- **Renal**: **acute glomerulonephritis (haematuria)**

## Investigations:

- Diagnosis is generally by **Mycoplasma serology**
- **Positive cold agglutination test**

- **Positive coombs** in 50 – 70% after 10 days of infection (it should be used with caution or not at all since 50% of the tests are false positive)
- Lack of bacteria in a gram-stained sputum.
- Lack of growth on blood agar.
- PCR.

## Management:

- **Clarithromycin** / Erythromycin.
- Tetracyclines such as **doxycycline** are an **alternative** if allergic/intolerant to macrolides/ fear of LQTS.

NB: Pneumococcus may also cause erythema multiforme.

The flu-like symptoms, slow progression of symptoms, bilateral consolidation, haemolytic anaemia and erythema multiforme point to a diagnosis of Mycoplasma. The most appropriate diagnostic test is Mycoplasma serology.

## HIV: Pneumocystis jiroveci pneumonia

Whilst the organism Pneumocystis carinii is now referred to as Pneumocystis jiroveci, the term Pneumocystis carinii pneumonia (PCP) is still in common use

- Pneumocystis jiroveci is a **unicellular eukaryote,** generally classified as a **fungus** but some authorities consider it a **protozoa.**
- Although PCP is officially a **fungal** infection it does not respond to anti-fungal medications.
- The organism is confined to the **alveolar space** of the lung and produces **debris** and **cysts** in the alveolar space with **interstitial** infiltration of lymphocytes and plasma cells so it can cause profound disturbance of O2 exchange and **fatal hypoxaemia** if left untreated.
- PCP >>> **Interstitial pneumonitis** with **foamy intra-alveolar** exudate.
- PCP is the most common opportunistic infection in **AIDS** and those **post-organ transplant (like post renal TX Pneumonia).**
- All patients with a **CD4 count < 200/mm³** should receive PCP prophylaxis.
- **Co-trimoxazole (TMP-SMX)** (Trimethoprim-Sulfamethoxazole) is the **first** line **prophylactic** agent.
- Prophylaxis should be used in immunosuppressed patients who are at risk of developing PCP: all those with a CD4 count of <200, patients started on high dose steroids, those on chemotherapeutic regimens associated with significant immunosuppression and post renal TX..

Clinically it presents with **several weeks' history** of Dyspnoea, Dry cough, Fever, **Very few chest signs (Normal chest auscultation)**, **typically, patients desaturate markedly on exertion.**

**Pneumothorax** is a common complication of PCP.

P.jiroveci can disseminate via the lymphatic and haematogenous routes to affect the thyroid, liver, bone marrow, lymph nodes and spleen.

**Extra pulmonary manifestations are rare (1-2% of cases), may cause:**

- Hepatosplenomegaly
- Lymphadenopathy
- Choroid lesions

## Investigation:

- CXR: **typically shows bilateral interstitial pulmonary infiltrates** but can present with other x-ray findings e.g. lobar consolidation. **May be normal CXR.**
- So **a normal chest x-ray does not exclude the diagnosis.**
- **Exercise-induced desaturation.**
- Sputum often fails to show PCP, bronchoalveolar lavage (**BAL**) often needed to demonstrate PCP (**silver** stain shows characteristic **cysts**).

**Definitive diagnosis** of PCP in HIV is by bronchial alveolar lavage (**BAL**) ± **Trans-bronchial biopsy** with **silver** staining which shows characteristic **cysts**.

**NB:** Open lung biopsy is gold standard, but rarely performed in clinical practice.

## Management:

- **Co-trimoxazole** oral or IV for 21 days in HIV +ve cases and less duration in other causes of immunosuppression.
- **IV pentamidine** in severe cases and if intolerant to co-trimoxazole.
- If resistant to TMP-SMX, the **combination of clindamycin and primaquine** is likely to be **more effective than** IV pentamidine.
- **Steroids if hypoxic** (**if pO2 < 9.3kPa** as steroids reduce risk of **respiratory failure** by 50% and death by a third).

**EX: Pregnant female** with **HIV + PCP** >>> treatment: **TMP-SMX**
TMP-SMX is the preferred initial therapy during pregnancy according to consensus guidelines.
The BNF states that there is a **teratogenic** risk in the 1st trimester (as **trimethoprim** is a folate antagonist), and neonatal haemolysis and methaemoglobinaemia in the 3rd trimester.
However, there is also considerable risk of harm to the foetus if the mother is unwell. The benefits in this situation therefore outweigh the risks, and it should be used.

## Eosinophilic pneumonia

- It is a **rare** respiratory pathology characterized by **pulmonary infiltrates** plus **pulmonary eosinophilia**.
- It can present acutely **AEP** (Acute Eosinophilic Pneumonia) over a few days or chronically **CEP** (Chronic Eosinophilic Pneumonia) over months to years.
- It can be **idiopathic** or **secondary** to parasites, drugs or vasculitis.
- **CEP** usually occurs in those aged in their **50s** with a **female** predominance.
- About 60% of patients with CEP have asthma and 90% are non-smoker.
- The peripheral eosinophilic count is **not** always raised.
- The **serum IgG** is raised in two-thirds and the **ESR** is elevated.
- **Sputum** and **BAL** often shown an **eosinophilia**.

**CXR**:

- **AEP**: bilateral diffuse infiltrates with effusion.
- **CEP**: bilateral dense **peripheral** infiltrates in the **OUTER** two-thirds of the lungs (i.e. often opposite to pulmonary oedema).

## Klebsiella

**Klebsiella pneumoniae** is a Gram-negative rod that is part of the normal gut flora. It can cause a number of infections in humans including pneumonia **(typically following aspiration)** and urinary tract infections.

### Features of Klebsiella pneumonia

- more common in **alcoholic and diabetics**
- may occur following aspiration
- 'red-currant jelly' sputum
- often affects upper lobes

## Prognosis

- commonly causes lung abscess formation and empyema
- mortality is 30-50%

A human neutrophil interacting with *Klebsiella pneumoniae* (pink), a multidrug-resistant bacterium that causes severe hospital infections. Credit: NIAID

# Psittacosis

Psittacosis is infection caused by *Chlamydia psittaci*. The most common presentation is as a cause of atypical pneumonia. Psittacosis should be suspected in a combination of typical fever with a **history of bird contact (reported in 84%)** or a presentation with pneumonia and severe headache or organomegaly and failure to respond to penicillin-based antibiotics.

## Epidemiology

- Psittacosis is present throughout the world, including the United Kingdom
- It is more common in young adults

## Pathology

- *Chlamydia psittaci* is an obligate intracellular bacterium
- Transmission is typically from birds or bird secretions including urine and faeces, typically occurring after cleaning bird cages
- Many birds have been implicated in transmission, including pet birds and wild birds
- Transmission from other animals or humans is possible but very rare and no strong female or male predisposition has been noted
- It is rare; in the US there are roughly 10 cases reported annually

### Patients typically present with a subacute onset of:

- Flu-like symptoms (90%): fever, headache and myalgia
- Respiratory symptoms (82%): dyspnoea, dry cough and chest pain

### Signs:

- Chest: unilateral crepitations and vesicular breathing (common), evidence of pleural effusion (uncommon)
- Abdomen: hepatomegaly and splenomegaly (rare)

### Investigations:

- Raised inflammatory markers
- Chest X-ray: consolidation (90%)
- Confirmation with serology (usually as part of atypical pneumonia screening)

### Treatment:

- 1st-line: tetracyclines e.g. doxycycline
- 2nd-line: macrolides e.g. erythromycin

## Lung abscess

A lung abscess is a well-circumscribed infection within the lung parenchyma.

### Pathophysiology

- most commonly forms secondary to aspiration pneumonia
  - poor dental hygiene, previous stroke and reduced consciousness are some of the risk factors for this
- other potential causes include:
  - haematogenous spread e.g. secondary to infective endocarditis
  - direct extension e.g. from an empyema
  - bronchial obstruction e.g. secondary from a lung tumour
- typically polymicrobial
- monomicrobial causes include:
  - Staphylococcus aureus
  - Klebsiella pneumonia
  - Pseudomonas aeruginosa

### Features

- similar features to pneumonia but generally runs a more subacute presentation
  - symptoms may develop over weeks
  - systemic features such as night sweats and weight loss may be seen

- fever
- productive cough
  - often foul-smelling sputum
  - haemoptysis in a minority of patients
- chest pain
- dyspnoea
- signs
  - dull percussion and bronchial breathing
  - clubbing may be seen

### Investigation

- **chest x-ray**
  - fluid-filled space within an area of consolidation
  - an air-fluid level is typically seen
- sputum and blood cultures should be obtained

### Management

- intravenous antibiotics
- if not resolving percutaneous drainage may be required and in very rare cases surgical resection

## Rheumatoid arthritis: respiratory manifestations

**A variety of respiratory problems may be seen in patients with rheumatoid arthritis:**

- pulmonary fibrosis
- pleural effusion
- pulmonary nodules
- bronchiolitis obliterans
- complications of drug therapy e.g. methotrexate pneumonitis
- pleurisy
- Caplan's syndrome - massive fibrotic nodules with occupational coal dust exposure
- infection (possibly atypical) secondary to immunosuppression

## Middle East respiratory syndrome

- **Middle East respiratory syndrome** (MERS) is caused by the betacoronavirus MERS-CoV.
- At the present time, MERS-CoV is limited to the Arabian Peninsula and its surrounding countries, although due to an incubation period of 2-14 days travellers returning from this region may present with MERS in other parts of the world.
- Contact with camels (including camel products such as milk) is a significant risk factor for MERS-CoV.
- The clinical syndrome of MERS is varied, ranging from very only mild symptoms through to life-threatening multi-organ failure.

## Tuberculosis

### Features

- Tuberculosis (TB) is the ninth leading cause of death worldwide (WHO). Pulmonary tuberculosis is an
- Infectious disease caused by **Mycobacterium tuberculosis.** Rarely, it may be due to Mycobacterium bovis or Mycobacterium africanum.
- In many cases, TB may remain dormant before it progresses to its active form. It most commonly involves the lungs and is communicable in this form, but may affect almost any organ system including the lymph nodes, CNS, liver, bones, genitourinary tract, and gastrointestinal tract.

### TB is a notifiable disease.

### Epidemiology

Tuberculosis mostly affects adults in their most productive years.
Over 95% of cases and deaths are in developing countries
In the US, an estimated 9.5 million people have latent TB infection

### Risk factors:

**Strong:**

- having lived in Asia, Latin America, Eastern Europe, or Africa for years
- Exposure to an infectious TB case
- People who are infected with HIV are 20 to 30 times more likely to develop active TB

- Immunocompromised individuals (diabetics, patients on immunosuppressive therapy,
- Malnourished, or those with haematological malignancies)
- Silicosis
- Apical fibrosis

**Weak:**

- Malignancy
- End-stage renal disease
- IV drug use
- Malnutrition
- Alcoholism
- Diabetes
- Congested residence i.e. nursing homes, homeless shelters etc..
- Smoking

## Key diagnostic features:

### Common

- Presence of risk factors (see above)
- Cough: initially dry later productive (50% of patients had cough over 2 weeks - 1)
- Low-grade fever. ~20% may have no fever.
- Night sweats, if present usually drenching
- Anorexia
- Malaise; may only be noticed in hindsight, after treatment

### Uncommon

- Pleuritic chest pain
- Haemoptysis; present in <10% patients (typically with advanced disease) - may be as a result of
- complication such as bronchiectasis and not representative of active disease.
- Dyspnoea; a late finding in the setting of extensive lung destruction or effusion
- Weight loss
- Psychological symptoms; depression or hypomania
- Patient may be asymptomatic and diagnosis made from coincidental findings or screening hypoadrenalism

## Signs:

Chest examination may be normal in mild/moderate disease. Possible findings include crackles,

bronchial breath sounds, or amphoric breath sounds (distant hollow breath sounds heard over cavities).
Clubbing - if longstanding disease
Erythema nodosum

## Investigations:

If there is clinical suspicion of TB, the patient should be isolated

**Chest x-ray**: Fibronodular opacities in upper lobes with or without cavitation.

**Sputum acid-fast bacilli** (AFB) smear (3 sputum samples): Positive for acid fast bacilli

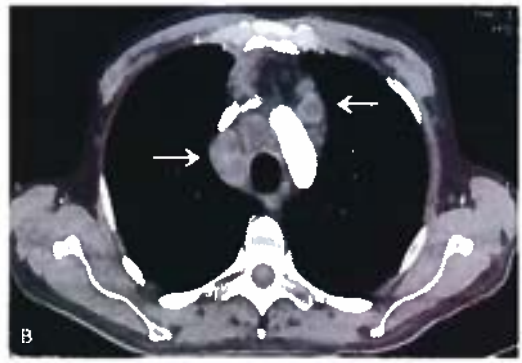
**Sputum culture**: most sensitive and specific test. Should always be performed: positive in TB

**FBC:** Raised WBC; low Hb

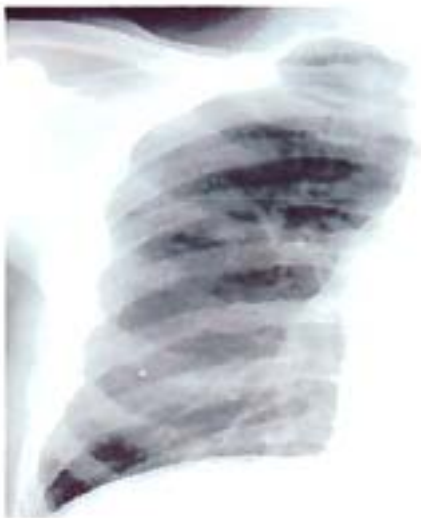
**Nucleic acid amplification tests (NAAT)**
on at least one of the sputum samples: positive for Mycobacterium tuberculosis.

**It is recommended that all patients with TB have an HIV test within 2 months of diagnosis of TB**

if the diagnosis is clinical then this should be stated




Typical presentation of a primary pulmonary tuberculosis infection in a 20-year-old man. **A.** Frontal chest radiograph shows mediastinal and right hilar lymphadenopathy (*black arrows*) and right upper lobe consolidation (*white arrow*). **B.** Contrast-enhanced CT demonstrates low-density enlarged mediastinal lymph nodes with rim peripheral enhancement consistent with necrotizing lymphadenopathy.



Primary tuberculosis may coalesce into a small granuloma in the upper lobe, referred to as a Ghon complex

The acid-fast bacilli of Mycobacterium tuberculosis seen with acid-fast staining at 100 power with oil immersion microscopy.

## People who should be screened for TB include:

- those born in high-incidence countries,
- HIV patients,
- intravenous drug users,
- health care workers who serve high-risk populations, and contacts of individuals with pulmonary TB.
- A tuberculin skin test or interferon gamma release assay are the standard methods for identifying persons infected with the mycobacterium.
- Screening persons other than high-risk population places a burden on resources and is therefore not recommended.

# Tuberculosis: Screening and Diagnosis

## Screening for latent tuberculosis

- The Mantoux test is the main technique used to screen for latent tuberculosis.
- In recent years the interferon-gamma blood test has also been introduced. It is used in a number of specific situations.

**such as:**

- the Mantoux test is positive or equivocal
- people where a tuberculin test may be falsely negative (see below)

## Mantoux test

- ml of 1:1,000 purified protein derivative (PPD) injected intradermally
- result read 2-3 days later
- Diameter of induration Positivity Interpretation
- < 6mm Negative - no significant
- hypersensitivity to tuberculin protein
- Previously unvaccinated individuals may be given the BCG
- 6 - 15mm Positive - hypersensitive to tuberculin proteinShould not be given BCG.
- May be due to previous TB infection or BCG > 15mm Strongly positive - strongly
- hypersensitive to tuberculin protein Suggests tuberculosis infection.

## False negative tests may be caused by:

- miliary TB
- sarcoidosis
- HIV
- lymphoma
- very young age (e.g. < 6 months)

## Heaf test

- The Heaf test was previously used in the UK but has been since been discontinued.
- It involved injection of PPD equivalent to 100,000 units per ml to the skin over the flexor surface of the left forearm. It was then read 3-10 days later.

# Diagnosis of active tuberculosis

## Chest x-ray

- upper lobe cavitation is the classical finding of reactivated TB bilateral hilar lymphadenopathy, and miliary type .

## Sputum smear

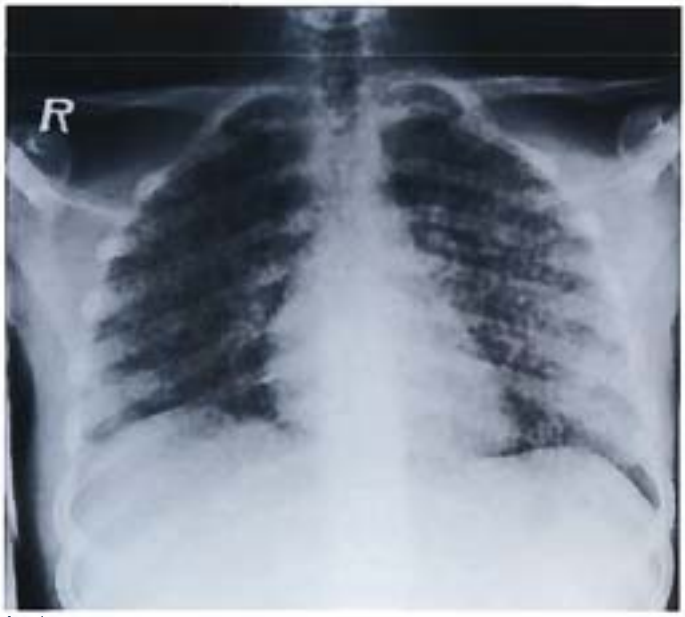
- 3 specimens are needed rapid and inexpensive test

stained for the presence of acid-fast bacilli (Ziehl-Neelsen stain)

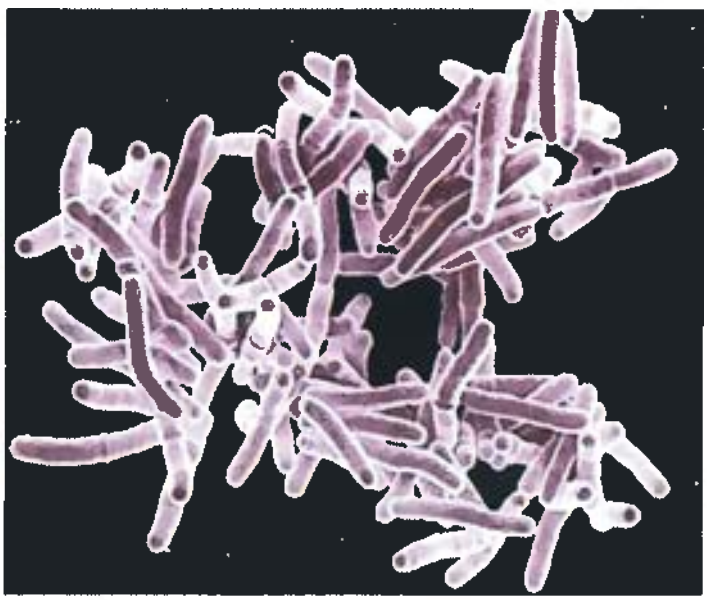
- all mycobacteria will stain positive (i.e. nontuberculous mycobacteria)

the sensitivity is between 50-80%

- this is decreased in individuals with HIV to around 20-30%




Miliary tuberculosis



Scanning electron micrograph of Mycobacterium tuberculosis bacteria, which cause TB.

### Sputum culture

- **the gold standard investigation**
  - more sensitive than a sputum smear and nucleic acid amplification tests
  - can assess drug sensitivities
  - can take 1-3 weeks (if using liquid media, longer if solid media)
- **Nucleic acid amplification tests (NAAT)**
  - allows rapid diagnosis (within 24-48 hours)
  - more sensitive than smear but less sensitive than culture

## Tuberculosis: Drug Therapy

### The standard therapy for treating active tuberculosis is:

- **Initial phase - first 2 months (RIPE)**
  - Rifampicin
  - Isoniazid
  - Pyrazinamide
  - Ethambutol (the 2006 NICE guidelines now recommend giving a 'fourth drug' such as ethambutol

**Routinely - previously this was only added if drug-resistant tuberculosis was suspected).**

- **Continuation phase - next 4 months**
  - Rifampicin
  - Isoniazid

**The treatment for latent tuberculosis is 3 months of isoniazid (with pyridoxine) and rifampicin OR 6 months of isoniazid (with pyridoxine)**

- Patients with meningeal tuberculosis are treated for a prolonged period (at least 12 months) with the addition of steroids

**Directly observed therapy(DOT) with a three times a week dosing regimen may be indicated in certain groups, including:**

- homeless people with active tuberculosis
- patients who are likely to have poor concordance
- all prisoners with active or latent tuberculosis

## Yellow nail syndrome (see pic)

The **nails** are yellow, thickened, curved, stop growing and may become detached from the nail bed.

It is characterised by the triad of **yellow discolouration of the nails, lymphedema** and **pleural effusions**.

Associated findings include **bronchiectasis in 40% of cases.**

## Lung fibrosis

### Fibrosis predominately affecting the upper zones

- **Extrinsic allergic alveolitis (EAA)**
- **Coal** worker's pneumoconiosis/progressive massive fibrosis
- **Tuberculosis**
- **S**arcoidosis
- Histiocytosis
- **S**ilicosis
- **A**nkylosing spondylitis (rare)
- **R**adiation

### Fibrosis predominately affecting the lower zones

- **Cryptogenic fibrosing alveolitis (IPF)**
- **Most connective tissue disorders** (**except** ankylosing spondylitis)
- **Drug**-induced: (see later).
- **Asbestosis**

It should be noted that **the more common causes** (**cryptogenic fibrosing alveolitis, drugs**) tend to affect the **lower** zones

**Histiocytosis X:** there is **pentalaminar X bodies** (Birbeck granules) found on **BAL** are considered diagnostic of pulmonary histiocytosis X.

### The drugs which can classically cause pulmonary fibrosis include:

- Cytotoxics: like: **Methotrexate**, **Cyclophosphamide, Bleomycin,** Busulphan
- Antibiotics: e.g. **Nitrofurantoin.**
- Cardiac drugs: **Amiodarone**, **Hydralazine,** tocainide.
- Opiates: e.g. **Heroin** abuse

- **Sulphasalazine pulmonary toxicity** is rare, but is increasingly recognised.
- **Gold**
- **Dosulepin (Prothiadine ®)** (TCA) is recognised as a very **rare** cause of pulmonary fibrosis.

## Treatment

- Drug withdrawal ± corticosteroids.

Penicillamine can be used in the treatment of pulmonary fibrosis.

Chest X-ray shows sub-pleural reticular opacities that increase from the apex to the bases of the lungs

CT scan showing advanced pulmonary fibrosis including 'honeycombing'

# Extrinsic allergic alveolitis (EAA) (Farmer lung) (HP)

Extrinsic allergic alveolitis (EAA, also known as **hypersensitivity pneumonitis)** (**HP**) is a condition caused by hypersensitivity induced lung damage due to a variety of inhaled organic particles.

It is thought to be largely caused by immune-complex mediated tissue damage (type **III** hypersensitivity) especially in **acute** phase, although delayed hypersensitivity (type **IV**) is also thought to play a role, especially in the **chronic** phase.

It is now very rare since the majority of farmers no longer bale hay in wet conditions. When present, it is most commonly associated **with positive Saccharopolyspora rectivirgula antibodies.**

## Examples:

- Pigeon **Bird** fanciers' lung: **avian** proteins
- **Farmers'** lung: spores of **Saccharopolyspora rectivirgula** (formerly Micropolyspora faeni) (NB: **Contaminated hay / straw** is the most common source of Saccharopolyspora rectivirgula which is responsible for Farmer's lung).
- **Malt** workers' lung: **Aspergillus clavatus**
- **Mushroom** workers' lung: thermophilic actinomycetes*
- Mouldy hay, mushroom compost, house dust, **hot/tub steam room** and contaminated water in the humidifiers.

Acute episodes are characterised by neutrophilic infiltration followed by lymphocytic infiltration and raised levels of interleukins 1 and 8 and TNF-alpha. This results in direct cellular damage and increased vascular permeability, which results in hypoxia and reduced lung compliance. Prolonged exposure leads to fibrosis and parenchymal destruction.

## Presentation:

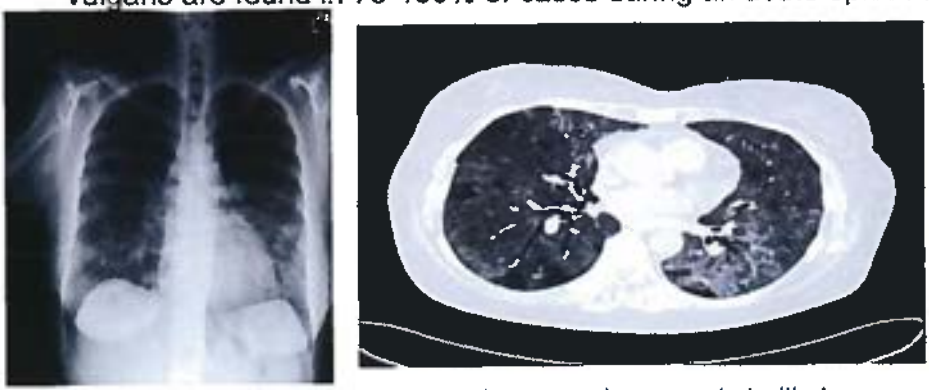
- Occur **4-8** hrs after exposure, SOB, dry cough, fever.
- O/E: **Bilateral basal fine inspiratory crackles**

## Investigation:

- CXR: **Upper** zone **fibrosis**
- BAL: lymphocytosis
- Blood: **NO eosinophilia**
- Circulating **IgG precipitant**: In farmer's lung >>> precipitins to Saccharopolyspora rectivirgula or Thermoactinomyces vulgaris are found in 75-100% of cases during an acute episode.

**EAA >>> NOT ALLERGY:**

- NO Eosinophilia
- NO ↑ IgE
- NO positive skin prick
- NO Antibiotics



Chest x-ray and CT scan from a middle-aged woman who presented with dyspnoea. The CT demonstrates multuple centrilobular ground glass nodules consistent with hypersensitivity pneumonitis

Positive serum avian **IgG** precipitins are **not diagnostic** of extrinsic allergic alveolitis (EAA), and only suggest the patient has had **old** exposure to birds.

## Treatment

- Primary treatment is **antigen avoidance** (change of job, repainting and ventilation in the steam room) , Then,
- **Systemic corticosteroids (Oral prednisolone).** Inhaled corticosteroids (ICS) are not as effective as oral corticosteroids.
- **NO** role for antibiotic therapy.

Although the aetiology is hypersensitivity to fungal spores, neither amphotericin B nor fluconazole are effective in the treatment of farmer's lung.

*here the terminology is slightly confusing as thermophilic actinomycetes is an umbrella term covering strains such as Micropolyspora faeni.

**Psittacosis** =
**Chlamydia psittaci pneumonia** is endemic in **birds including** psittacine birds, canaries, finches, pigeons and poultry.
Pet owners, vets and zoo keepers are most at risk.
It is **rare** in **children**.
**Person to person transmission** occurs especially in a hospital environment.
**Sputum** Gram stain reveals a **few** leucocytes and no predominant bacteria. There are few signs and few laboratory/x ray findings.
It is characterized by **relative bradycardia** with non-specific chest signs, coupled with diffuse CXR changes like widespread hazy opacities affecting both **lower** lobes, a **low TLC** and **abnormal LFTs** are consistent with the disease.

Positive serology is with complement-fixing antibodies.
**Serum avian precipitins** is **positive**.
**Tetracyclines** are the antibiotics of choice.

# Idiopathic pulmonary fibrosis (IPF)

Idiopathic pulmonary fibrosis, (previously termed **cryptogenic fibrosing alveolitis),** is a chronic lung condition characterised by progressive fibrosis of the interstitium of the lungs.

Whilst there are many causes of lung fibrosis (secondary fibrosing alveolitis) (e.g. medications, connective tissue disease, SLE, sarcoidosis, asbestos, pneumoconiosis).

However, the term IPF is reserved when no underlying cause exists.

IPF is typically seen in patients aged **50-70 years** and is twice as common in **men**.

## Features:

- **Progressive exertional dyspnoea**
- **Bilateral fine basal crackles** on auscultation
- **Clubbing**
- Dry cough
- PFT shows **restrictive** lung spirometry with the **reduced TLCO and KCO.**

There are **no satisfactory treatment options** for **idiopathic pulmonary fibrosis (IPF) = (Usual Interstitial Pneumonia (UIP).**
It is necessary to distinguish UIP from non-specific interstitial pneumonia (NSIP) as this is more steroid-responsive.
HRCT chest is very important for differentiating UIP from NSIP.
**Bronchoalveolar lavage (BAL) lymphocytosis** predicts a **better corticosteroid response** than the typical BAL neutrophilia.

## Diagnosis:

- Spirometry: classically a **restrictive** picture (FEV1 normal/decreased, FVC decreased, FEV1/FVC increased).
- Impaired gas exchange: **reduced transfer factor (TLCO).**
- **CXR: bilateral interstitial shadowing** (typically **small, irregular, peripheral opacities - 'ground-glass' in lower zones - later progressing to 'honeycombing').**
- **HRCT:** High-resolution CT scanning is the investigation of **choice** and required to make a diagnosis of IPF
    a. A predominant **reticular** pattern on HRCT is consistent with UIP and correlates with irreversible fibrosis.
    b. The **ground glass** appearance often associated with NSIP indicates inflammation, which may be responsive to steroids.
- **ANA** positive in 30%, **RF** positive in 10% but this does not necessarily mean that the fibrosis is secondary to a connective tissue disease. Titres are usually low

## Management:

- Pulmonary rehabilitation
- Supplementary **oxygen (LTOT).**
- Lung transplantation.
- There is some evidence that pirfenidone (an anti-fibrotic agent) may be useful in selected patients.
- Other options under clinical trials include interferon-gamma 1beta and Bosentan.

- **Unfortunately** responsiveness to corticosteroids in idiopathic pulmonary fibrosis is **poor**, although up to **20%** may show some objective response with respect to stabilisation of lung function. Whilst only 20% of patients may be steroid responsive, other treatments include azathioprine and cyclophosphamide.

The chance for IPF of this being responsive to corticosteroids is **1:5** which depends on **Bronchoalveolar lavage BAL lymphocytosis.**

### Prognosis:

- **Poor**, average life expectancy is around 3-4 years

**EX**: A **male** patient about **55** years old has recently been diagnosed with **idiopathic pulmonary fibrosis**, he wants to know if he is suitable for steroid therapy >> It depends on **BAL lymphocytosis** >> **good steroid response**.

## Lymphoid interstitial pneumonia

### Presentation:

- **gradual onset breathlessness over** considerable time about 2 years, **intermittent fevers**, **weight loss** and **inspiratory crackles**.
- There is mild **anaemia** and **high immunoglobulins**.
- CXR: diffuse **lower** zone alveolar **shadowing**.
- Lung Biopsy: diffuse **lymphoid interstitial infiltrates**.
- PFT: **restrictive** pattern.
- It is usually associated with **HIV (IV drug abusers)**, **connective** tissue disease, **HBV** infection, chronic active hepatitis and **Hashimoto's thyroiditis**.

## Sarcoidosis

- Sarcoidosis is a **multisystem** disorder of unknown aetiology characterised by **non-caseating granulomas**.
- It is more common in young adults and in people of **African** descent.
- Prevalence varies amongst different ethnic populations; in Europe, sarcoid is commonest amongst **Caucasians** and has a significantly higher incidence in the **Irish**.
- This non-caseating granulomas may occur **anywhere**.
- These granulomas have the capacity to produce **1, 25 vitamin D** explaining the associated hypercalcaemia.
- This has a **good prognosis** and usually **resolves spontaneously** over 6 to 8 weeks.

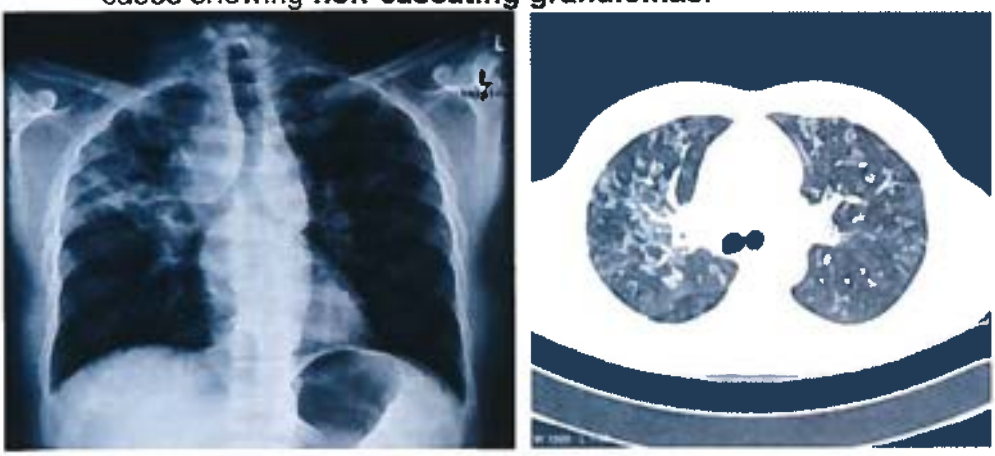
- However, **TB should be excluded** by sending sputum or BAL washings for AFB.
- The tuberculin test is negative in approximately 80-90 % of sarcoidosis cases, but its rule in diagnosis is controversial.
- Inflammatory **arthritis** in sarcoidosis typically targets the **ankle** joint.

**Sarcoidosis remits without treatment in approximately two-thirds of people.**

**There is no one diagnostic test for sarcoidosis** and hence diagnosis is still largely **clinical.**

## Investigations:

1) **HRCT chest:**
   - It can demonstrate the degree of fibrosis, micronodules in a subpleural or bronchoalveolar distribution, fissural nodularity and bronchial distortion.
   - Irregular linear opacities and ground-glass shadowing may also be seen.
   - If the CT scan is diagnostic, then mediastinoscopy, bronchoscopy or biopsies can often be avoided.
2) **Trans-bronchial biopsy** (Tissue biopsy): It is the **definitive route to confirming the diagnosis** and positive results are seen in **90%** of cases showing **non-caseating granulomas.**



Chest x-ray and CT scan showing **stage 2** sarcoidosis with both bilateral hilar lymphadenopathy + interstitial infiltrates. The reticulonodular opacities are particularly noted in the upper zones. Remember that pulmonary fibrosis (which this case has not yet progressed to) may be divided into conditions which predominately affect the upper zones and those which predominately affect the lower zones - sarcoidosis is one of the former. The CT of the chest demonstrates diffuse areas of nodularity predominantly in a peri bronchial distribution with patchy areas of consolidation particularly in the upper lobes. There is some surrounding ground glass opacities. No gross reticular changes to suggest fibrosis.

## Other investigations:

- **Chest x ray** which is abnormal in **90%** of lung sarcoidosis, but 30-60% are asymptomatic (that is, incidental CXR finding). So sarcoidosis is often picked up on routine CXR.
- **ACE levels:**
  - It is elevated in about **70%** of patients with active sarcoidosis.
  - It have a sensitivity of 60% and specificity of 70% and are therefore not reliable in the diagnosis of sarcoidosis.
  - It is not a diagnostic test.
  - It is best used to assess the **response** of steroid therapy.
  - It have a role in monitoring disease **activity** as it reflects macrophages activity.
  - It is not specific as it can be elevated in patients with histoplasmosis, Miliary TB, Gaucher's, lymphoma or, hepatitis, liver diseases (as in liver disease, slow the metabolic excretion of serum ACE and so increased ACE activity.
  - A normal serum ACE would not exclude the diagnosis.
  - Increased ACE in CSF may be useful in diagnosis of CNS sarcoidosis.
  - Tissue ACE activity is highest in sarcoid LN rather than in pulmonary tissues.
- Routine bloods may show **hypercalcaemia** (seen in **10%** if patients) and it is due to overproduction of vitamin D by sarcoid granulomas and a raised ESR.
- Leukopenia in 5-10% of patients.
- **Hypergammaglobulinaemia** (↑ Immunoglobulins) in 30-80%.
- Spirometry: may show a restrictive defect, decreased compliance and impaired diffusion capacity.
- Gallium-67 scan - not used routinely
- **The Kveim test** (where part of the spleen or LN extracts from a patient with known sarcoidosis is injected under the skin) with a granulomatous reaction appearing 4 weeks after intradermal injection, which is no longer performed due to concerns about cross-infection, it is positive in 50-60% of patients.
- Cardiac sarcoidosis is rare but can manifest as a **prolonged PR interval.**

**A CXR may show the following changes:**

- Stage 0 = normal
- Stage 1 = Bilateral hilar lymphadenopathy (BHL)
- Stage 2 = BHL + interstitial infiltrates
- Stage 3 = Diffuse interstitial infiltrates only
- Stage 4 = Diffuse fibrosis

**Sarcoidosis CXR**
- 1 = BHL
- 2 = BHL + infiltrates
- 3 = Infiltrates only
- 4 = Fibrosis

## Treatment:

- **Prednisolone** is the mainstay of initial treatment for sarcoidosis, continued **for 12 months** or more in those patients who respond, but tapered to the minimal effective dose to stop within 2 years maximum.
- Most patients achieve remission within 2 years.
- Methotrexate and hydroxychloroquine may be added as steroid sparing agents.

## Indications for steroids treatment:

- **Hypercalcaemia.**
- Worsening lung function.
- **Eye** (bilateral posterior uveitis is common eye manifestation)
- Heart or neuro involvement.

## Prognostic features:

Factors associated with **poor prognosis**☹

- Age of onset >40 years
- **Insidious onset**, symptoms > 6 months
- **Absence of erythema nodosum**
- **Extra pulmonary** manifestations: e.g. splenomegaly, **lupus pernio** (is a chronic raised purplish indurated hard lesion of the skin)
- CXR: **stage III-IV features**
- **Black** people (**Afro**-Caribbean or **Afro**-American race)
- **Cardiac** involvement
- Neuro-sarcoidosis
- Chronic **hypercalcaemia**
- Nasal mucosal involvement

Erythema nodosum is associated with a good prognosis in sarcoidosis

**Mikulicz syndrome:**
It is a chronic condition characterized by the abnormal enlargement of **parotids**, **lacrimal** and **salivary** glands. The **tonsils** and other glands in the soft tissue of the face and neck may also be involved. It is associated with sarcoidosis.

## Lofgren's syndrome

- Lofgren's syndrome is an **benign acute form sarcoidosis** characterised by:
  1) Bilateral hilar lymphadenopathy **(BHL),**
  2) **Erythema nodosum (EN),**
  3) **Fever**
  4) **Polyarthralgia.**
- It typically occurs in **young females** and carries an **excellent prognosis** and the development of chronic disease is rare.
- So if you suspect, **follow up** appointment with **CXR** in **3** months

**NB**: **Loffler's syndrome** is a cause of pulmonary **eosinophilia** with **bronchospasm**, **abdominal** discomfort and **urticarial rash** thought to be caused by parasites such as **Ascaris** lumbricoides, **Strongyloides.**
**Heerfordt's syndrome** is an **acute** presentation of sarcoidosis, which presents with **fever**, **uveitis** (red, painful eyes), **bilateral** swelling of the **parotid** and **other salivary and lacrimal glands**. **Facial nerve palsy** (**LMNL**) may be a feature, and other features of sarcoidosis may co-exist (e.g. skin lesions, pulmonary involvement).

As it represents a form of **neuro-sarcoidosis**, other neurological features may be present (e.g. meningism, ophthalmoplegia and pupillary reflex dysfunction).

# Bilateral hilar lymphadenopathy (BHL)

The most common causes of bilateral hilar lymphadenopathy (BHL) (Bulky mediastinum) are **Sarcoidosis** and **Tuberculosis.**

## Other causes include:

- **Lymphoma**/other malignancy.
- **Pneumoconiosis** e.g. **Berylliosis**
- **Fungi** e.g. histoplas**mosis**, coccidioidomyc**osis**

**NB**: Amyloid**osis** is not commonly associated with bilateral hilar lymphadenopathy

# Pneumoconiosis

Pneumoconiosis is a chronic reaction of the lung parenchyma as a consequence of **chronic dust inhalation**

**Pneumoconiosis is an x ray diagnosis.**

| | |
|---|---|
| **Coal** | Multiple small round opacities, typically 1-10 mm in diameter, mostly in the upper lobes |
| **Asbestos** | Pleural plaques and fibrosis more marked in the lower zones |
| **Silica** | Multiple small nodules scattered diffusely throughout the lungs and egg-shell calcification of the hilar nodes |
| **Beryllium** | Acute pneumonitis that may continue to a granulomatous reaction (compare with sarcoidosis) with lymphadenopathy |
| **Iron dust** | Nodular pulmonary pattern with greater density but with less marked fibrosis |

Typical CXR appearance of the different dust particles are listed below:

# Berylliosis

Exposure to **beryllium** is seen in the **nuclear** power, **telecommunications**, semi-conductor and **electronics** industries. مهندس اليكترونيات وذرات

It results in a similar clinical picture to that of **sarcoidosis**.

The lung histology shows **non-caseating granulomatosis.**

**EX**: A 53-year-old man presents to the respiratory clinic. He has been involved in **nuclear power plant construction** for much of his life and has increasing shortness of breath and chronic cough over the past 12 months.
CXR shows **bilateral hilar lymphadenopathy.**
Which of the following is the most likely diagnosis? >>> **Berylliosis**
In this case it is the patient's occupation that pushes us towards berylliosis as the most appropriate answer.
Sarcoidosis is the major differential here, but it is the possible exposure to beryllium because of occupation which points us away from this as the most likely diagnosis.

# Silicosis

**Silicosis is a risk factor for developing TB** (silica is toxic to macrophages).

Silicosis is a fibrotic lung disease associated with the inhalation of silicon dioxide (silica).
It is usually found in quarry workers or miners and also sandblasters, **pottery** workers and **stone masons** (if the dust contains quartz).

## Features:

- **Fibrosing** lung disease (**UPPER** zone).
- The pathognomic radiological changes: **'egg-shell' calcification** of the **hilar lymph nodes.**

Diagnosis of silicosis is made on industrial history and typical CXR changes.

Chest x-ray from a patient with silicosis. Note the bilateral diffuse upper lobe reticular shadowing superimposed with occasional scattered mass like opacities. These features are in keeping with silicosis and progressive massive fibrosis (PMF)

CT scan from a patient with silicosis showing upper zone predominant mass-like scarring with calcification and volume loss. Hilar and mediastinal lymph node calcification also noted. No cavitary changes are seen. There is a left pleural effusion.

# Asbestos and the lung

Asbestos can cause a variety of lung disease from benign pleural plaques to mesothelioma:

## Pleural plaques:

- Pleural plaques are **benign** and do not undergo malignant change.
- They are **the most common form** of asbestos related lung disease and generally occur **after a latent period of 20-40 years**.
- It does not become apparent until 20 years or more after exposure.
- Pleural plaques are not precursors of malignant change, but they reflect previous asbestos exposure.

## Pleural thickening:

- Asbestos exposure may cause **diffuse pleural thickening** in a similar pattern to that seen following an **empyema** or **haemothorax**.

## Asbestosis:

- The **severity** of asbestosis is **related to the length of exposure** (as in working in the **boiler** industry, **plumber**).
- The **latent period** is typically **15-30 years**. The onset of asbestosis is typically over 20 years following exposure.
- Asbestosis typically causes **lower** lobe **fibrosis**.

**Pleural effusions / thickening** may result from **acute** asbestos pleurisy.

- As with other forms of lung fibrosis the most common symptoms are shortness-of-breath and reduced exercise tolerance.
- There is no specific treatment for asbestosis. Further exposure should be avoided, and patients should be vaccinated against pneumococcus and influenza.
- Patients should be advised to stop smoking (if they do) and long-term oxygen therapy (LTOT) may be required.

## Mesothelioma:

- Mesothelioma is a **malignant** disease of the pleura.
- There are 3 types of asbestos: blue, brown and white.
- **Crocidolite (blue) and brown asbestos** is the most dangerous form.
- Mesothelioma dose not usually develop **until 10-50 years after exposure to_asbestos** and for this reason it is often difficult to discover the exact cause.

- Rarely, mesothelioma develops in people who have never exposed to asbestos.
- Significant previous **radiation exposure** has also a significant aetiology in some cases of malignant mesothelioma.
- Research has **not** found any evidence that **smoking** increases a person's risk of developing mesothelioma, also exposure to **other** building materials such as **fiberglass** does **not** increase the risk.

## Possible features:

- Progressive shortness-of-breath
- Chest pain
- Pleural effusion

If suspect Mesothelioma >>> **Thoracoscopy** with **drainage** and **biopsy.**

**Diagnosis of mesothelioma is by Thoracoscopy and biopsy**
Tissue can be obtained from thoracoscopy with biopsy from abnormal looking areas, as such this is **the most appropriate investigation** to deliver the diagnosis.

Blind pleural biopsy may result in tissue being obtained from an area not affected by mesothelioma. As such this is not correct.

Whilst thoracentesis is likely to obtain malignant cells, the histopathologist may not be able to type them adequately.

CT scanning may reveal structural abnormalities but will not give a histological diagnosis and sputum cytology would be unlikely to reveal malignant cells.

Pleural effusion in mesothelioma tends to have normal LDH and < 1000 WBCs /ml.

But if the effusion has **less glucose, high protein** with ↑ WBCs mainly **lymphocytes** >>> so think of **tuberculous effusion**

Patients are usually offered **palliative chemotherapy** and there is also a limited role for surgery and radiotherapy.

Unfortunately the **prognosis is very poor,** with a median survival from diagnosis of 8-14 months.

## Lung cancer:

- Asbestos exposure is a risk factor for lung cancer and also has a synergistic effect with cigarette smoke.

# Pulmonary embolism (PE)

**NICE guidelines 2020**

**Please refer to NICE VISUAL SUMMARY FOR PE AND DVT**

All patients with symptoms or signs suggestive of a PE should have a history taken, examination performed and a chest x-ray to exclude other pathology.

If a PE is still suspected a two-level PE **Wells score** should be performed:

| Clinical feature | Points |
|---|---|
| **Clinical** signs and symptoms of DVT (minimum of **leg** swelling and pain with palpation of the deep veins) | 3 |
| An alternative diagnosis is less likely than PE (**PE** is #1 diagnosis, or equally likely) | 3 |
| **HR** > 100 /min | 1.5 |
| **Immobilisation** for more than **3 days** or **surgery** in the previous **4 weeks** | 1.5 |
| **Previous** DVT/PE | 1.5 |
| **Haemoptysis** | 1 |
| **Malignancy** (on treatment, treated in the last 6 months, or palliative) | 1 |

It is important to note the **minor and major risk factors** for PE/VTE (BTS):

| Minor risk factors (with a relative risk of 2-4) | Major risk factors (relative risk 5-20) |
|---|---|
| • **Oral contraceptive pill**<br>• Occult malignancy<br>• Long distance travel<br>• Thrombotic disorder.<br>• HTN<br>• CHF | • Lower limb problems including a **fracture** or **varicose veins**.<br>• Post-operative ICU stay.<br>• Abdominal/pelvic or advanced **malignancy**<br>• **Previous VTE**, and<br>• **Pregnancy**. |

## Traditional interpretation:

- High score: >6.0
- Moderate score: 2.0 to 6.0
- Low score: <2.0

## Clinical probability simplified scores

- PE **likely: (> 4)**: more than 4 points >>> Consider diagnostic imaging.
- PE **unlikely: (≤ 4)**: 4 points or less >>> Consider D-dimer to R/O PE.

If a PE is 'likely' (more than 4 points) arrange an immediate computed tomography pulmonary angiogram (**CTPA**). If there is a delay in getting the CTPA then gives **LMWH** until the scan is performed.

If a PE is 'unlikely' (4 points or less) arranged a **D-dimer** test. If this is positive arrange an immediate computed tomography pulmonary angiogram (**CTPA**). If there is a delay in getting the CTPA then gives **LMWH** until the scan is performed.

If the patient has an allergy to contrast media or renal impairment a V/Q scan should be used instead of a CTPA.

PE >>>> tachycardia, **tachypnea, low grade fever** with **normal CXR.**

## D-dimers:

- **Sensitivity = 95-98%, but poor specificity**
- **It is good -ve test** (i.e. if –ve >>> so exclude PE, if +ve >>> not specific for PE may be due to other causes rather than PE) (already high in pregnancy>>>useless).
- Most D-dimer assays have a **high negative predictive value (NPV)** (approximately 90%). (NPV is the probability that the patient does not have the disease given a negative test result, that is, if the test is negative they are unlikely to have the disease.)
- However the positive predictive value (PPV) is often low (approximately 15%). (PPV is the probability that the patient will have a condition given a positive test result, that is, in the case of D-dimer a positive result does not correlate with a high probability of disease). The test is therefore **useful to exclude DVT rather than to confirm DVT**.
- Current evidence strongly supports the use of a D-dimer assay in the clinical algorithm of suspected DVT. In other words, the clinical likelihood of a DVT should be taken into account when interpreting the results of the D-dimer assay.

## ECG:

- The classic ECG changes seen in PE are a large S wave in lead I, a large Q wave in lead III and an inverted T wave in lead III - **'S1Q3T3'.** However this change is seen in no more than **20%** of patients.
- RBBB and right axis deviation are also associated with PE.
- **Sinus tachycardia** may also be seen.

## V/Q scan:

- **Xenon** is used for imaging **ventilation**, whilst technetium labelled macroaggregated human serum albumin (**MAA**) is used to image **perfusion**.
- No use of iodine so it is not contraindicated in iodine hypersensitivity.
- **Sensitivity = 98%; but a specificity = 40%** - high negative predictive value, i.e., **if normal perfusion virtually excludes PE**
- Other causes of mismatch in V/Q include old pulmonary embolisms, AV malformations, vasculitis, and previous radiotherapy.
- **COPD** gives matched defects.
- **In mitral valve disease** >> Increased pulmonary venous pressure >> **increased** perfusion flow to the **upper** lobes.
- Radiation to the foetus is small. It is **not contraindicated in pregnancy**, although the perfusion only scan is adequate.
- V/Q scanning carries a slightly increased risk of **childhood cancer** compared with CTPA (1/280,000 versus less than 1/1,000,000).

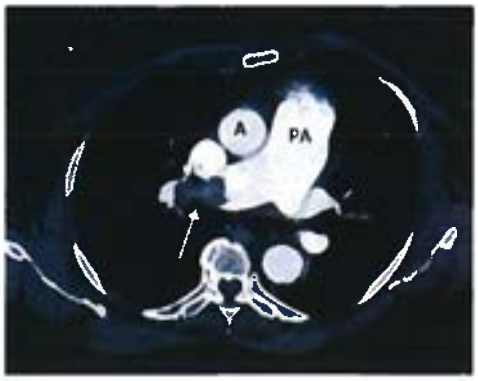
## CTPA:

- Peripheral emboli affecting subsegmental arteries may be missed

## Pulmonary angiography:

- **The gold standard**
- oSignificant complication rate compared to other investigations

## CTPA or V/Q scans?




Acute pulmonary embolism with likely pulmonary arterial hypertension. There is an intraluminal filling defect, consistent with an acute pulmonary embolism (*white arrow*). The pulmonary arterial trunk (*PA*) is larger than the adjacent ascending aorta (*A*), suggesting pulmonary arterial hypertension, likely due to the large PE.

Pulmonary angiogram showing abruptly truncated pulmonary arteries associated with regions of diminished perfusion typical of chronic pulmonary emboli

The British Thoracic Society (BTS) published guidelines on the management of patients with suspected pulmonary embolism (PE).
Key points from the guidelines include:

- Computed tomographic pulmonary angiography (**CTPA**) **is now the recommended initial lung-imaging modality for non-massive PE.**

Pulmonary embolism >>>> **CTPA** is **first**-line investigation

- Advantages compared to V/Q scans include speed, easier to perform out-of-hours, a reduced need for further imaging and the possibility of providing an alternative diagnosis if PE is excluded.
- **If the CTPA is negative** then patients do **not** need further investigations or treatment for PE.
- **V/Q scanning** may be **used initially if** appropriate facilities exist, the chest x-ray is normal, and there is no significant symptomatic concurrent cardiopulmonary disease.
- It is still common in UK hospitals, despite guidelines, for a ventilation-perfusion scan to be done first-line.

## Pregnancy: DVT/PE investigation

Guidelines were updated by the Royal College of Obstetricians. Key points include:

- **Chest x-ray should be performed in all patients (with abdominal shield).**
- **Compression duplex Doppler should be performed if the chest x-ray is normal** - this may provide indirect evidence of a pulmonary embolism as both conditions require anticoagulation **this may negate the need for further radiation exposure.** But it does not exclude asymptomatic proximal venous thrombosis.
- **D-dimer is of limited use** in the investigation of thromboembolism as it often raised in pregnancy.
- Echocardiography may show acute right sided dilatation, but this is by no means diagnostic.
- The decision to perform a V/Q or CTPA should be taken at a **local level** after discussion with the patient and radiologist:

**Comparing CTPA to V/Q scanning in pregnancy:**

| CTPA | V/Q scanning |
|---|---|
| CTPA slightly increases the lifetime risk of **maternal breast cancer** (increased by up to 13.6%, background risk of 1/200 for study population). **Pregnancy makes breast tissue particularly sensitive to the effects of radiation.** | V/Q scanning carries a slightly increased risk of **childhood cancer** compared with CTPA (1/280,000 versus less than 1/1,000,000) |

In the **pregnancy** situation with probability of PE >>> **the optimal way to exclude PE** is >>> **Half dose V/Q scan.**
If **low** probability of PE >>> discharge and follow up
If **high** probability of PE >>> LMWH

Initially estimation of **pre-test probability** by senior staff
Then **D-Dimer**, if further investigation is needed, so
Then **CXR** is the next step in absence of leg signs.
If there is no leg signs, so progress to **CXR and CTPA** if clinical suspicious is very high.
But in the presence of leg signs, **bilateral leg Doppler US** can be performed.
If leg Doppler is positive, CXR then CTPA are the next recommended steps.

## Pulmonary embolism: management

**The NICE guidelines of 2020** provided some clarity on how long patients should be anticoagulated for after a pulmonary embolism (PE). Selected points are listed below.

Low molecular weight heparin (LMWH) or fondaparinux should be given **initially after a PE is diagnosed.**

An exception to this is for patients with a massive PE where **thrombolysis** is being considered. In such a situation unfractionated heparin should be used.

- A vitamin K antagonist (i.e., **warfarin**) should be **given within 24 hours of the diagnosis.**
- The LMWH or fondaparinux should be continued **for at least 5 days or until the** international normalised ratio **(INR) is 2.0 or above for at least 48 hours,** whichever is longer, **i.e. LMWH or fondaparinux is given at the same time with warfarin until the INR is in the therapeutic range**
- Warfarin should be continued **for at least 3 months**. At 3 months, NICE advise that clinicians should 'assess the risks and benefits of extending treatment'
- NICE advice extending warfarin **beyond 3 months for patients with unprovoked PE.** This essentially means that **if there was no obvious cause or provoking factor** (surgery, trauma, significant immobility) it may imply the patient has a **tendency to thrombosis** and should be given treatment **longer than the norm of 3 months. (i.e. Pt. with PE of no cause >>>> warfarin for 6 months)**.
- For patients with active **cancer** NICE recommend using **LMWH for 6 months.**

## Thrombolysis:

- Thrombolysis is now recommended as the first-line treatment for **massive PE where there is circulatory failure** (e.g. hypotension or arrest PEA). Other invasive approaches should be considered where appropriate facilities exist

Massive PE + cardiopulmonary arrest (PEA) >>>>>> **IV thrombolysis**, then **followed by CPR** for **90** minutes.

## In acute major PE with low BP >>>

- **IV fluids** should be given firstly to increase RV filling pressure and maintain COP.
- **Heparinisation** will prevent further emboli occurring.
- If hypotension is severe and do not respond to plasma expanders, Use **inotropic** support.
- **Thrombolysis** should be considered if the patient is not improving after 15-30 minutes with the above measures.
- **Pulmonary embolectomy** should only be undertaken when thrombolysis is contraindicated.

# Fat embolism

The appearance of **multiple petechiae** in the distribution of the **axilla** or **upper body** is characteristic of a fat embolism.

The petechial rash is **pathognomonic** of this syndrome, but **only** occurs in **30-50%** of cases.

Unlike emboli that arise from a thrombus, fat emboli are **small** and **multiple** producing **widespread** effects. They may occur **1 to 3 days** following a **fracture** and are more common in **closed** fractures on the **long** bones or **pelvis** like femur.

**The clinical features of fat emboli are predominately:**

1) **Pulmonary** (shortness of breath, hypoxia)
2) **Neurological** (confusion and agitation)
3) **Dermatological** (petechiae) and
4) **Haematological** (thrombocytopenia, anaemia).

**EX**: A 31-year-old motorcyclist becomes **confused** and **dyspnoeic** on the orthopaedic ward 24 hours after fracturing his right **femur** in an accident.

Which of the following **skin** lesions may be found on examination? Fat embolism >>> Multiple petechiae in both axilla.

# Pneumothorax

The British Thoracic Society (BTS) published updated guidelines for the management of spontaneous pneumothorax in.

A pneumothorax is termed primary if there is no underlying lung disease and **secondary** if there is (like **asthma**, COPD).

If Pt. has asthma >>>>> treat as secondary pneumothorax

## Primary pneumothorax:

- If the rim of air is < 2cm and the patient is not short of breath then **discharge** should be considered and review in the clinic in 2 to 3 wks.
- Otherwise **aspiration** should be attempted.
- If this fails (defined as > 2 cm or still short of breath) then **a chest drain** should be inserted.
- If following aspiration, the rim of air is < 2cm and the breathing has improved then discharge should be considered with outpatient review.

## Secondary pneumothorax:

- If the patient is > 50 years old and the rim of air is **> 2cm** and/or the patient is short of breath then a chest drain should be inserted.
- Otherwise, **aspiration** should be attempted if the rim of air is **between 1-2cm**. Even if successful the patient should be admitted and observed for at least 24 hours. If aspiration fails (i.e. pneumothorax is still greater than 1cm) a chest drain should be inserted. All patients should be admitted for at least 24 hours.
- If the pneumothorax is **less the 1cm** then the BTS guidelines suggest giving **oxygen** and **admitting for 24 hours.**
- **NB: Regarding scuba diving,** the BTS guidelines state: 'Diving should be **permanently avoided** unless the patient has undergone bilateral surgical pleurectomy and has normal lung function and chest CT scan postoperatively.'
- **NB: Air travel** is acceptable once the pneumothorax has fully resolved (Pt. can't air travel for **2 wk. post complete aspiration of the air**).
- Unlike a primary pneumothorax, a secondary pneumothorax always requires intervention.
- It is preferable the insertion of a **small bore chest drain (8-14 SWG)** as there are no advantages in the insertion of a large bore chest drain (>20 FG) as it usually more painful and delays discharge.

- The most appropriate point for chest drains insertion is in **the 'safe triangle' in the mid-axillary line**. This reduces the chance of injury to the internal mammary artery, muscle, liver and spleen.

Atmospheric air drops during flights and increases in deep sea diving can cause recurrence of pneumothorax. This is due to expansion and rupture of pulmonary blebs. Many commercial airlines previously advised a **6-week** interval between pneumothorax and air travel, but this has now been amended to **1 week** following full resolution.

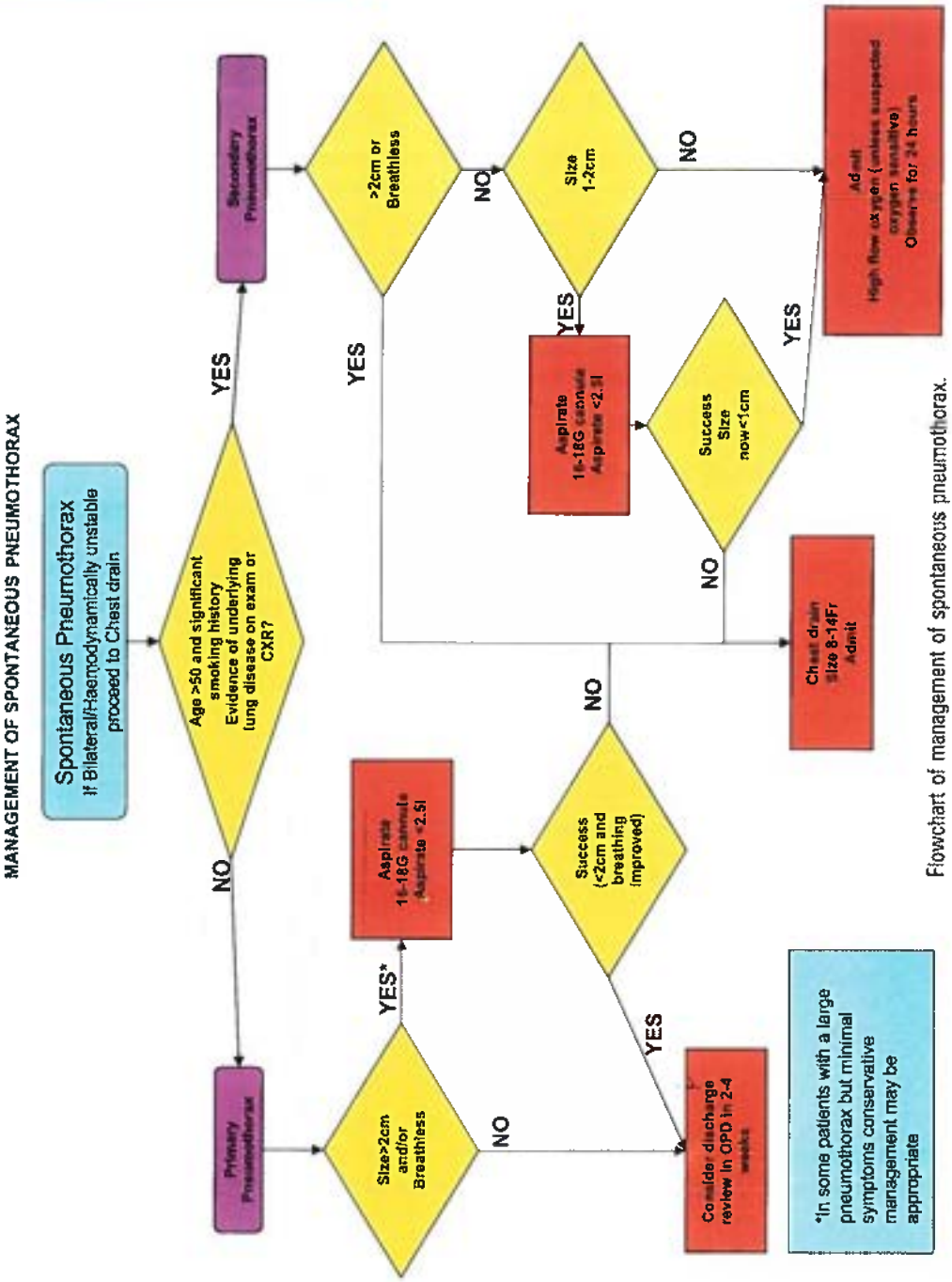
However, the British Thoracic Society emphasises that **the recurrence risk only significantly falls after 1 year**, and therefore in the absence of a definitive surgical procedure patients might wish to defer travel until then.

## Iatrogenic pneumothorax:

- **Less** likelihood of recurrence than spontaneous pneumothorax.
- Majority will resolve with observation, if treatment is required then aspiration should be used.
- Ventilated patients need chest drains, as may some patients with COPD.

**NB**: **Hamman's sign** (or **'crunch'**) is a crunching **systolic** sound heard over the sternal edge in mediastinal emphysema or left apical pneumothoraces.

It can be dependent on the patient's position when auscultating.




Flowchart of management of spontaneous pneumothorax.

**NB**: Questions sometimes discuss the size of the pneumothorax in **percentage** terms rather than giving the **interpleural distance**. A variety of formulas have been proposed to convert between the two.

**As a very general rule of thumb:**

| Average interpleural distance | Approximate size of pneumothorax |
|---|---|
| 0.5 cm | 10% |
| 1 cm | 15 % |
| 2 cm | 30% |
| 3 cm | 45% |
| 4 cm | 60% |

**EX**. A 1ry pneumothorax of 20% if therefore within the 2 cm limit >>> so for observation, if there is no shortness of breath.

The management of choice for a **second unilateral pneumothorax** in a **fit individual** is referral to a **thoracic surgeon for bullectomy and pleurectomy**, this is conducted under **VATS** (Video Assisted Thoracoscopic Surgery).

Until then, activities such as diving and flying are contraindicated.

**Pleurodesis** could be considered in **elderly** or **frail** individuals, but is not suitable in young fit patient.

As his lung has re-expanded after ICT, there will be no broncho-pleural fistula.

## Video Assisted Thoracoscopic Surgery (VATS)

### Video Assisted Thoracoscopic Surgery is indicated in:

- **Second time ipsilateral** pneumothorax
- **Bilateral spontaneous** pneumothorax
- **Spontaneous haemothorax**
- **Persistent air leak** (more than 5 to 7 days of drainage)
- Certain occupations, for example, pilots or divers.

# Pleural effusion

The British Thoracic Society (BTS) produced guidelines in 2010 covering the investigation of patients with a pleural effusion.

## Investigations

### Imaging:

- posterioranterior (PA) chest x-rays should be performed in all patients
- ultrasound is recommended: it increases the likelihood of successful pleural aspiration and is sensitive for detecting pleural fluid septations
- contrast CT is now increasingly performed to investigate the underlying cause, particularly for exudative effusions

### Pleural aspiration:

- As above, ultrasound is recommended to reduce the complication rate.
- A **21G** needle and 50ml syringe should be used.
- Fluid should be sent for pH, protein, lactate dehydrogenase (LDH), cytology and microbiology

### Exudate (> 30g/L protein):

- Infection: pneumonia, TB, sub-phrenic abscess
- Connective tissue disease: RA, SLE
- Neoplasia: lung cancer, mesothelioma, metastases
- Pancreatitis
- Pulmonary embolism
- Dressler's syndrome
- Yellow nail syndrome: It is very rare, affects adults, also known as Primary lymphedema, It is pleural effusion associated with yellow dystrophic nails + bronchiectasis (in 40%), also associated with chronic sinusitis and persistent cough.

### Transudate (< 30g/L protein):

- **Heart** failure
- Hypoalbuminaemia (**liver** disease, **nephrotic** syndrome, malabsorption)
- **Hypothyroidism**
- **Meigs' syndrome** (a triad of: Ascites+ Rt. pleural effusion + benign ovarian tumour fibroma). It resolves after the resection of the tumour.

**Light's criteria** were developed in 1972 to help distinguish between a transudate and an exudate. The BTS recommend using the criteria for borderline cases:

- Exudates have a protein level of >30 g/L,
- Transudates have a protein level of <30 g/L

- If the protein level is between 25-35 g/L ight's criteria should be applied.
- An **exudate** is likely if at least **one** of the following criteria are met:
  - Pleural fluid protein divided by serum protein **>0.5**
  - Pleural fluid LDH divided by serum LDH **>0.6**
  - Pleural fluid LDH more than two-thirds the upper limits of normal serum LDH

**Raised LDH** >>> Inflammatory **exudate**.

### Other characteristic pleural fluid findings:

- Low glucose: T.B, Rheumatoid arthritis
- Raised amylase: pancreatitis, oesophageal perforation
- Heavy blood staining: mesothelioma, pulmonary embolism, tuberculosis
- **Uniform blood staining** throughout pleural fluid samples: **Malignancy**
- **Low pleural PH less than 7.2 >>> Empyema,** inflammatory effusion related to **RA, TB, malignancy and oesophageal rupture.**

**The pleural glucose level is low:** Levels less than **3.3** mmol/L are found in:

- Empyema
- Tuberculosis
- Malignancy
- Rheumatoid arthritis
- Lupus
- Oesophageal rupture

## Management of recurrent pleural effusion

Options for managing patients with recurrent pleural effusions include:

- recurrent aspiration
- pleurodesis
- indwelling pleural catheter
- drug management to alleviate symptoms e.g. opioids to relieve dyspnoea

In a unilateral pleural effusion, which in the clinical setting may represent an empyema.
It is therefore critical that you urgently obtain a **sample of pleural fluid** to confirm or exclude this, as an **empyema** requires a **chest drain** to be inserted. If pus is obtained, a chest drain should be inserted.
Other fluid should be tested for **pH**, and if **less than 7.2** this indicates an empyema and a drain should again be inserted.

Fluid should also be sent for **protein** and **LDH** (to determine if it is a **transudate** or **exudate**), glucose, gram stain, microscopy, culture and sensitivity and cytology.
Current UK best practice guidelines indicate US should be used to guide pleural aspiration, but US alone is unlikely to add further information.
Sputum cultures, whilst useful, will take at least 3-5 days to yield diagnostic information and pleural aspiration is therefore more critical at this stage.
**Unilateral** pleural effusion >>> **Diagnostic pleural fluid sampling ± drain**, **CT Thorax** should be considered to rule out tumours.

**NB**: **Head and neck or oesophageal or cardiothoracic surgery** (even neck LN excision) can cause **damage to thoracic duct**, which can lead to **chylous formation** (whitish milky pleural effusion) about 4 litres of fluids per day to leak into the pleural space, so large pleural effusion. To confirm the diagnosis, you can test the effusion for **lipase** or **triglycerides**.
**Pleural triglyceride level more than 1.2 mmol/l** >>> indicate a 99% chance that this is **chylous** pleural effusion.

## Chest drain

A chest drain is a tube inserted into the pleural cavity which creates a one-way valve, allowing movement of air or liquid out of the cavity.

**Chest drain insertion is indicated in cases of:**

- Pleural effusion
- Pneumothorax not suitable for conservative management or aspiration
- Empyema
- Haemothorax
- Haemopneumothorax
- Chylothorax
- In some cases of penetrating chest wall injury in ventilated patients

**Insertion of a chest drain** is relatively contraindicated in patients with any of the following:

- INR > 1.3
- Platelet count < 75
- Pulmonary bullae
- Pleural adhesions

**Please** note, all of the above represent only relative contraindications, addressing respiratory compromise in an emergency situation should always be on an individual case basis.
**Once** patient consent has been obtained and patient imaging assessed, the patient should be positioned in a supine position or at a 45° angle.

The patient's forearm may be positioned behind the patient's head to allow easy access to the axilla.
Identify the 5th intercostal space in the midaxillary line.
Alternatively, positioning may be determined by ultrasound guidance, British Thoracic Society Guidance 'strongly recommend' use of ultrasound guidance in all cases of fluid within the pleura.
The area should be anaesthetised using local anaesthetic injection (lidocaine, up to 3mg/kg).
The drainage tube should then be inserted using a Seldinger technique.
The drain tubing should then be secured using either a straight stitch or with an adhesive dressing.
**Positioning** can be confirmed by aspiration of fluid from the drainage tubing, by 'swinging' of the fluid within the drain tubing when the patient inspires and on chest x-ray.
**Complications** that may occur and which the patient should be advised of in the process of obtaining consent:

- Failure of insertion - the drain may be abutting the apical pleura, in which case it should be pulled back, or may be subcutaneous or in rare cases could enter the abdominal cavity. In both latter cases, the drain should be removed and re-sited.
- Bleeding - around the site of the drain or into the pleural space
- Infection
- Penetration of the lung
- Re-expansion pulmonary oedema

**Re-expansion** pulmonary oedema may be preceded by the onset of a cough and/or shortness of breath.
In the event of concerns regarding re-expansion pulmonary oedema, the chest drain should be clamped and an urgent chest x-ray should be obtained.
To avoid re-expansion pulmonary oedema, it is recommended that the drain tubing should be clamped regularly in the event of rapid fluid output i.e. drain output should not exceed 1L of fluid over a short period of time (less than 6 hours).
**Removal** of the chest drain is dependent upon the indication for insertion:

- In cases of fluid drainage from the pleural cavity, the drain should be removed when there has been no output for > 24 hours and imaging shows resolution of the fluid collection.
- In cases of pneumothorax, the drain should be removed when it is no longer bubbling spontaneously or when the patient coughs and ideally when imaging shows resolution of the pneumothorax.
- Drains inserted in cases of penetrating chest injury should be reviewed by the specialist to confirm an appropriate time for removal.

# Chest x-ray: cavitating lung lesion

## Differential

- **Tuberculosis**
- **Fungal** infections: **Aspergillosis, Histoplasmosis**, Coccidioidomycosis
- **Malignancy: Squamous cell lung cancer**
- Lung **abscess** (Staph aureus, Klebsiella and Pseudomonas)
- **Wegener's** granulomatosis
- **Lung infarction: Pulmonary embolism**
- Rheumatoid arthritis

EX: Old pt. + **DM** + CXR: cavitating apical shadow >>> **TB** >>> **Sputum AFB**, If pt. unable to produce sputum >>> **bronchoscopy** + **BAL** for TB

EX: A 45-year-old **seaman** presents with cough and fever. A CXR demonstrates a **cavitating** lung lesion.

Which of the following is the most likely cause? >>> **Histoplasmosis.**

Histoplasmosis normally evolves slowly over as long as 20 years but may follow a more rapid course in the immunocompromised (seamen may be more prone to sexually transmitted diseases **STDs** such as **HIV**).

# Pulmonary hypertension: causes and classification

Pulmonary hypertension may be defined as a sustained elevation in mean pulmonary arterial pressure of greater than 25 mmHg at rest. It has recently been reclassified by the WHO:

**Group 1:** Pulmonary arterial hypertension (PAH)

- idiopathic*
- familial
- associated conditions: collagen vascular disease, congenital heart disease with systemic to pulmonary shunts, HIV**, drugs and toxins, sickle cell disease
- persistent pulmonary hypertension of the newborn

**Group 2**: Pulmonary hypertension with left heart disease

- left-sided atrial, ventricular or valvular disease such as left ventricular systolic and diastolic dysfunction, mitral stenosis and mitral regurgitation

**Group 3**: Pulmonary hypertension secondary to lung disease/hypoxia
- COPD
- interstitial lung disease
- sleep apnoea
- high altitude

**Group 4**: Pulmonary hypertension due to thromboembolic disease

**Group 5:** Miscellaneous conditions
- lymphangiomatosis e.g. secondary to carcinomatosis or sarcoidosis

*previously termed primary pulmonary hypertension
**the mechanism by which HIV infection produces pulmonary hypertension remains unknown

*salicylate overdose leads to a mixed respiratory alkalosis and metabolic acidosis. **Early stimulation of the respiratory centre leads to a respiratory alkalosis** whilst later the direct acid effects of salicylates (combined with acute renal failure) may lead to an acidosis

# Lung cancer

## Background:

It is well known that the incidence of **adenocarcinoma** is **rising** in comparison to the **other** types of non-small cell lung cancer.

| |
|---|
| **Adenocarcinoma** is now the most common type of lung cancer in the **USA**. |
| In the **UK**, **Squamous cell cancer** remains **the most common subtype.** |

### Lung cancer:
- **Squamous**: **35%**
- Adenocarcinoma: 30%
- Small (oat) cell: 15%
- Large cell: 10%
- Other: 5%

### Other tumours:
- Alveolar cell carcinoma: not related to smoking, ++sputum
- Bronchial adenoma: mostly carcinoid

## Lung cancer: risk factors

### Smoking
- Increases risk of lung can by a factor of **10**

**Other factors:**

- **Asbestos** - increases risk of lung ca by a factor of **5**
- Arsenic
- Radon
- Nickel
- Chromate
- Aromatic hydrocarbon
- Cryptogenic fibrosing alveolitis

**Factors** that are **NOT** related

- **Coal dust**

**NB**: Smoking and asbestos are synergistic, i.e. a smoker with asbestos exposure has a 10 x 5 = 50 times increased risk

**NB:** Whilst many chemicals have been implicated in the development of lung cancer **passive smoking** is the most likely cause. Up to **15%** of lung cancers in patients who do not smoke are thought to be caused by passive smoking.

## Investigation

**Chest x-ray:**

- this is often the first investigation done in patients with suspected lung cancer
- in **around 10% of patients subsequently diagnosed with lung cancer the chest x-ray was reported as normal**

**CT:** is the investigation of choice to investigate suspected lung cancer

**Bronchoscopy:**

- this allows a biopsy to be taken to obtain a histological diagnosis sometimes aided by endobronchial ultrasound

**PET scanning**

- is typically done in non-small cell lung cancer to establish eligibility for curative treatment
- uses 18-fluorodeoxygenase which is preferentially taken up by neoplastic tissue
- has been shown to improve diagnostic sensitivity of both local and distant metastasis spread in non-small cell lung cancer

**Bloods:** raised platelets may be seen

**NB**: The most appropriate tool to confirm the diagnosis of bronchial carcinoma is >>> **Bronchoscopy ± Trans bronchial biopsy** (**NOT** CT-guided FNA biopsy).

# Non-small cell lung cancer (NSCLC)

There are **three** main subtypes of non-small cell lung cancer:

## 1) Squamous cell cancer:

- Typically central
- Associated with parathyroid hormone-related protein (PTHrP) secretion → **hypercalcaemia.**
- Hyperthyroidism due to **ectopic TSH**
- Strongly associated with finger **clubbing.**
- Hypertrophic pulmonary osteoarthropathy (**HPOA**)

**HPOA** is seen in patients with bronchial carcinoma.

It may **pre-date** the discovery of the underlying lesion.

It is characterised by **finger clubbing** and **long bone pain** (**tender wrists without synovitis** i.e. without stiffness, without limitation of movements).

The most sensitive diagnostic investigation is **isotope bone scan**: **increase** in the **uptake** in **long bones**, **around periarticular surfaces**, and also **mandible** and **scapulae**.
**X-Ray**: **Periosteitis over the ulna and radius**.

## 2) Adenocarcinoma:

- Most common type of lung cancer in **non-smokers,** although the majority of patients who develop lung adenocarcinoma are smokers.
- Typically located on the lung **periphery.**
- **Normal bronchoscopy.**
- **Gynaecomastia.**

**PET/CT scan** offers the best imaging modality to determine **LN** involvement in **bronchial adenocarcinoma.**

Lung adenocarcinoma:
- Most common type in non-smokers
- Peripheral lesion
- Normal bronchoscopy
- Gynecomastia

NB: **Bronchoalveolar cell carcinoma** classically presents with progressive breathlessness and the production of large amounts of sputum (**bronchorrhoea**). They account for up to 1% of all bronchial carcinomas.

The tumour spreads using the alveolar walls as a frame and the alveoli are often filled with mucin.

## 3) Large cell lung carcinoma:

### Management of Non-small cell lung cancer:

- Only 20% suitable for surgery.
- Prognosis after surgery is about 50-67% at 5 years with stage 1disease
- Mediastinoscopy performed prior to surgery as CT does not always show mediastinal lymph node involvement.
- Curative or palliative radiotherapy.
- Poor response to chemotherapy.
- Survival advantages for combined radio and chemo therapy

### Surgery contraindications of Non-small cell lung cancer:

- Assess general health (age ≥ 70 yrs., IHD, **MI within 6 wks.**, ↑ PCO2, etc.).
- Stage IIIb or IV (i.e. **metastases** present).
- FEV1 < 1.5 litres is considered a general cut-off point*: as it means that there will be insufficient respiratory reserve post-surgery.
- MALIGNANT pleural effusion
- Tumour near hilum
- Vocal cord paralysis (It implies extracapsular spread to mediastinal nodes and is an indication of inoperability).
- SVC obstruction (SVCO)

* However if FEV1 **< 1.5 L for lobectomy** or **< 2.0 L for pneumonectomy** then some authorities advocate further lung function tests as operations may still go ahead based on the results

Any Pt with malignancy or even disseminated malignancy and unknown primary, presents with oedema of the arms and face, persistent headache, with dilated neck veins >>> you suspect superior vena cava obstruction (SVCO).

Up to 4% of patients with lung cancer will develop SVCO at some point during their disease. Up to 10% of SCLC will present with SVCO.

**Both Non-small** cell cancer and **small** cell malignancy may cause SVCO.

SVCO is much more likely to be associated with **right sided lung lesion 4** times than with left sided lesions.

**SVCO** >>> It is an **oncological emergency**.
CXR is abnormal in around 85% of cases, mediastinal widening is common.
Mediastinal **radiotherapy** leads to **symptomatic relief** in **80% of patients**, although case studies have shown this does not always correlate to patency of the superior vena cava.
Radiotherapy is useful but its effects are **not quick** enough.
If possible, an attempt should be made to obtain a **tissue diagnosis**, as some tumours respond to radiotherapy whereas others are more sensitive to chemotherapy.
Tumours which are very chemosensitive, such as germ cell and lymphoma, can cause SVCO.
**Dexamethasone IV** at **high** dose is of benefit in **severe** cases of SVCO + **LMWH**.
It is important to note that in 2004 NICE recommended considering **stenting** in the majority of cases of SVCO. This is a **minimally invasive** procedure which **relieves** symptoms **quicker than** chemotherapy or radiotherapy.
**SVCO >>> immediate management >>> Dexamethasone IV + LMWH.**

## Small (oat) cell lung cancer (SCLC)

### Features:

- Usually **central**
- Arise from **APUD*** cells
- Ectopic **ADH** → hyponatraemia
- Ectopic **ACTH** → ACTH secretion can cause **bilateral adrenal hyperplasia, Cushing's** syndrome (not typical, hypertension, hyperglycaemia, **hypokalaemia, alkalosis, hirsutism** and muscle weakness are more common than buffalo hump etc.)
- **Lambert-Eaton syndrome:** antibodies to voltage gated calcium channels (VGCC) causing **myasthenic** like syndrome.

**EX:** Male pt. chronic heavy smoker with chest infection plus hyperglycaemia + ↓ **K** + ↑ HCO3 >>> should suspect **SCLC** with **ectopic ACTH secretion**.

**But** if with ↓Na and ↑**K** >>> think of **Adrenal metastasis** >>> **MRI adrenals**.

### The following are adverse prognostic factors in small cell lung cancer:

- Serum Na < 132 mmol/l
- Weight loss > 10%
- WHO performance status > 2
- Alkaline phosphatase > 1.5 times upper limit of normal
- LDH > 1.5 times upper limit of normal
- Extensive disease (occurring outside one hemithorax and ipsilateral supraclavicular fossa nodes).

## Management:

- **Usually metastatic disease by time of diagnosis**
- **Surgery**: it has **little** role, only used for debulking
- Most patients with limited disease now receive a **combination of chemotherapy and radiotherapy**
- Patients with more extensive disease are offered palliative **chemotherapy.**
- Prognosis for small cell cancer despite chemotherapy is little - 10% at 5 years.

**APUD*** cells an acronym for:
- **Amine** - high amine content
- **Precursor Uptake** - high uptake of amine precursors
- **Decarboxylase** - high content of the enzyme decarboxylase

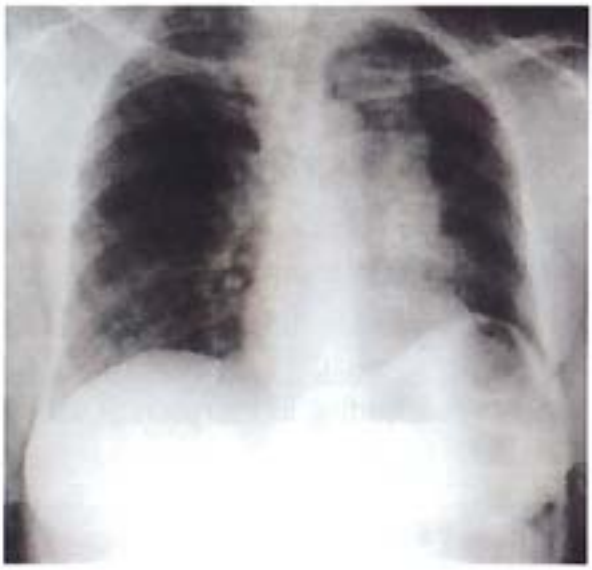
**Non-small** NSCLC >>> **Radiotherapy**
**Small** SCLC >>> **Chemotherapy**

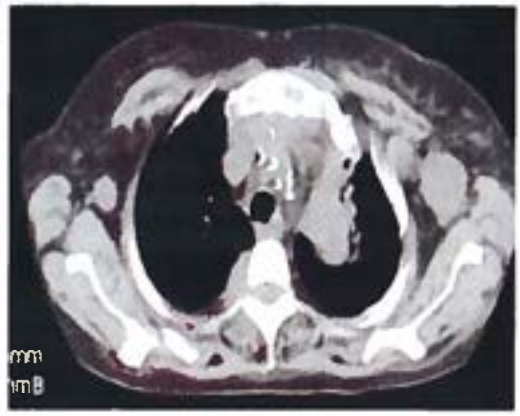
Overall 5 year survival for lung cancer patients is still of the order of **14%**. (American Cancer Society 1998). i.e Overall lung cancer survival is less than 15% at five years.

This contrasts with approximately 50% for cancer of the breast and around 70% for cancer of the cervix.

## Bronchial Carcinoma

- 20-30% of cases with bronchial carcinoma are of **small (oat) cell type** from endocrine **K**- cells (**Kulchitsky**) cells.
- Primary bronchial cancer >>> the tumour edge may have **a fluffy or spiked appearance.**
- Paraneoplastic manifestations:
  - SIADH (5 - 10%)
  - ACTH (5 %)
  - ANP





Chest X-ray showing squamous cell carcinoma of the lung. **B.** CT scan demonstrating the architecture of the squamous cell carcinoma of the lung.

## Stage grouping by TMN subset

| Nodes \ Tumour | T1 | T2 | T3 | T4 |
|---|---|---|---|---|
| N0 | IA | IB | IIB | IIIB |
| N1 | IIA | IIB | IIIA | IIIB |
| N2 | IIIA | IIIA | IIIA | IIIB |
| N3 | IIIB | IIIB | IIIB | IIIB |

| Key | |
|---|---|
| | Patient should be offered surgery if no medical contraindications and adequate lung function |
| | Surgery may be suitable for some patients, based on clinical judgement |
| | Not suitable for surgery |

**EX**: T3N1MX = stage III A

## Lung cancer: Paraneoplastic features

Paraneoplastic syndromes are a result of antibody generation from or against malignant cells attacking normal tissue.

Both non-small cell and **small** cell lung cancers are associated with Paraneoplastic syndromes, although they are more common with the latter due to its neuroendocrine cell origin.

Examples include **anti-neuronal antibodies** (anti-Hu, anti-Yo, anti-Ri) directed **against the Purkinje cells** of the **cerebellum** leading to the **cerebellar syndrome** (ataxia).

The **Lambert-Eaton myasthenic syndrome (LEMS)** is a pre-synaptic disorder of auto-antibody IgG directed against the **pre**-synaptic voltage gated **calcium** channel (VGCC) leading to **impaired acetylcholine release**. Clinically, patients present with **proximal muscle weakness/ wasting** that **improves** with **exercise**.

Symptomatic hyponatraemia due to **SIADH** is treated with demeclocycline which induces nephrogenic diabetes insipidus leading to excretion of excess water.

**Lambert- Eaton syndrome** is characterised by:
1) Proximal muscle weakness (the cranial nerves and respiratory muscles are usually spared)
2) Depressed or absent tendon reflexes and
3) Autonomic features (for example, dry mouth, impotence, etc).
70% of cases are due to **small cell lung cancer**.
Unlike myasthenia gravis, **improved by exercise** which is associated with increasing muscle strength and there is a negative response to Tensilon. **Electromyography** is useful in confirming the diagnosis where repeated nerve stimulations cause a progressive increase in the size of the muscle action potential.
**Eaton** (1905-1958) U.S. neurologist at Mayo Clinic. **Lambert** (1915-2003) U.S neuro-physiologist at Mayo Clinic and Prof. of physiology at University of Minnesota.

**Paraneoplastic features of lung cancer:**
- **Squamous cell**: PTHrp, TSH, Clubbing, HPOA
- **Adenocarcinoma:** Gynaecomastia
- **Small cell:** ADH, ACTH, Lambert-Eaton syndrome
- **Bronchial carcinoma:** SIADH, ACTH, ANP

**EX**: A 49-year-old man is diagnosed with **small cell lung cancer** + progressive truncal **ataxia** + **Normal brain MRI** >>>> **Paraneoplastic syndromes** >>> Diagnosis by: **Anti-Purkinje cell antibody levels**

**EX**: Male pt. 50 years old chronic heavy smoker with several episodes of haemoptysis, he is grossly oedematous, ascites, Hb=10, Ceat=180, albumin=22. Urine protein +++, 5 gm proteinuria/day >>>? **Bronchial carcinoma** with **membranous GN** >> **BX**: **thickened glomerular BM** with **deposits of IgG and C3**.

## Carcinoid Lung cancer:

- The vast majority of **bronchial adenomas** are **carcinoid tumours**, arising from the amine precursor uptake and decarboxylation **(APUD)** system, like small cell tumours.
- Lung carcinoid accounts 1% of lung tumours and for 10% of carcinoid tumours.
- Classical carcinoid syndrome occurs in less than 10% of patients with carcinoid tumours, but occurs most commonly in those with tumours of the small intestine, appendix and proximal small bowel.
- Those in the lung rarely cause carcinoid, but have been associated with **ACTH secretion** and subsequent **Cushing's syndrome.**
- Other associated conditions where foregut carcinoid tumours are found in the pancreas are associated with Zollinger-Ellison syndrome and VIPoma.
- Carcinoid tumours are the most common neuroendocrine tumours, and usually originate in the **enterochromaffin** cells.
- The most common location is the **GIT**, but that can also occur in the bronchi and lungs.
- Carcinoid tumours of the lung (bronchial adenomas) (also called **argentafinomas** as they take up **silver**) are neuroendocrine cells and are **derived** from the **K cells (Kulchitsky) in the lung.**
- The masses are typically **silent**, but they can present due to **ectopic hormone** secretion or carcinoid heart disease.
- The carcinoid syndrome presents in approximately 10% of cases, more commonly those with GI tract primaries, and is predominantly due to release of 5-HT.
- The term bronchial adenoma is being phased out.

## Lung carcinoid:

- Typical age = **40-50 years**
- The carcinoid syndrome characterised by **Skin flushing, bronchospasm, diarrhoea,** and **right-sided valvular heart lesions.**
- **Smoking NOT** risk factor
- **Slow growing:** e.g. **long history of cough, recurrent haemoptysis**
- Chest pain, breathlessness, wheeze and cough are less common.
- It accounts for between 1-5% of all lung tumours.
- Often **centrally** located and not seen on CXR
- It is usually occur in the major bronchi, 85% can be seen bronchoscopically.
- A carcinoid tumour in the left lower lobe bronchus could cause distal **collapse** of the left lower lobe.

- **'Cherry red ball'** is a typical finding that often seen on **bronchoscopy** (Bronchoscopy identifies up to 80% of carcinoid tumours in the main bronchi. It is a **highly vascular** 'cherry-like' tumour causing recurrent haemoptysis and bronchial obstruction.
- Biopsy is usually followed with brisk **bleeding** and should be done via **rigid** bronchoscopy).
- Carcinoid syndrome itself is rare (usually associated with **liver metastases**)
- **Plasma chromograffin A** is an effective **screening** test for carcinoid as it is very sensitive, but it is not specific.
- **24 hour urinary excretion of 5-hydroxyindoleacetic acid (5HIAA)** is more **specific** for the diagnosis, but false positives and negatives are present.

## Management:

- **Surgical resection:** is the treatment of choice.
- But somatostatin analogues can be used where this is not possible.
- If no metastases then 90% survival at 5 years.

**EX:** A 38-year-old man presents with a 2 week history of recurrent haemoptysis which he has noted over the last 18 months. He is unaware of any chest pain and is a light smoker of five cigarettes daily. A CXR reveals collapse of the left lower lobe.
What is the most likely diagnosis? **>>> Bronchial carcinoid**

**EX:** A 40-year-old man is undergoing investigation for acromegaly. MRI of the pituitary fossa is normal, but a routine chest x ray reveals a large centrally based mass. The patient is a non-smoker.

What is the most likely type of this lung tumour >>> **Carcinoid Lung cancer,** which is secreting **GHRH** and resulting in **acromegaly**

**EX:** Young female + 4 month history of cough productive of mucoid sputum streaked with bright red blood + wheezing + diarrhoea >>>? **Carcinoid tumour >>> Bronchoscopy.**

The diagnosis of **phrenic nerve palsy** is suspected when on the CXR the **diaphragmatic leaflet is elevated** and is confirmed by **fluoroscopy** by observing **paradoxical diaphragmatic motion of the affected side** on sniff and cough.
In patients with normal lungs unilateral paralysis is usually asymptomatic and rarely requires treatment.

## Lung cancer: referral

The 2015 NICE cancer referral guidelines gave the following advice:

Refer people using a suspected cancer pathway referral (for an appointment within 2 weeks) for lung cancer if they:

- have chest x-ray findings that suggest lung cancer
- are aged 40 and over with unexplained haemoptysis

Offer an urgent chest x-ray (to be performed within 2 weeks) to assess for lung cancer in people aged 40 and over if they have 2 or more of the following unexplained symptoms, or if they have ever smoked and have 1 or more of the following unexplained symptoms:

- cough
- fatigue
- shortness of breath
- chest pain
- weight loss
- appetite loss

Consider an urgent chest x-ray (to be performed within 2 weeks) to assess for lung cancer in people aged 40 and over with any of the following:

- persistent or recurrent chest infection
- finger clubbing
- supraclavicular lymphadenopathy or persistent cervical lymphadenopathy
- chest signs consistent with lung cancer
- thrombocytosis

## lung metastases

**Lung metastases are seen with a wide variety of cancers including:**

- breast cancer
- colorectal cancer
- renal cell cancer
- bladder cancer
- prostate cancer

Multiple, round well-defined lung secondaries are often referred to as 'cannonball metastases'. They are most commonly seen with renal cell cancer but may also occur secondary to choriocarcinoma and prostate cancer.

**Calcification in lung metastases is uncommon** except in the case of chondrosarcoma or osteosarcoma.

Chest x-ray showing **cannonball metastases** secondary to renal cell cancer. Multiple well defined nodules are noted distributed in both lung fields

## Bronchiolitis

Bronchiolitis is a condition characterised by acute bronchiolar inflammation. Respiratory syncytial virus (RSV) is the pathogen in 75-80% of cases.

### Epidemiology

- most common cause of a serious lower respiratory tract infection in < 1yr olds (90% are 1-9 months, with a peak incidence of 3-6 months). Maternal IgG provides protection to newborns against RSV
- higher incidence in winter

### Basics

- respiratory syncytial virus (RSV) is the pathogen in 75-80% of cases
- other causes: mycoplasma, adenoviruses
- may be secondary bacterial infection
- more serious if bronchopulmonary dysplasia (e.g. Premature), congenital heart disease or cystic fibrosis

## Features

- coryzal symptoms (including mild fever) precede:
- dry cough
- increasing breathlessness
- wheezing, fine inspiratory crackles (not always present)
- feeding difficulties associated with increasing dyspnoea are often the reason for hospital admission

## NICE recommend immediate referral if they have any of the following:

- apnea (observed or reported)
- child looks seriously unwell to a healthcare professional
- severe respiratory distress, for example grunting, marked chest recession, or a respiratory rate of over 70 breaths/minute
- central cyanosis
- persistent oxygen saturation of less than 92% when breathing air.

### NICE recommend that clinicians 'consider' referring to hospital if any of the following apply:

- a respiratory rate of over 60 breaths/minute
- difficulty with breastfeeding or inadequate oral fluid intake (50-75% of usual volume 'taking account of risk factors and using clinical judgement')
- clinical dehydration.

## Investigation

- immunofluorescence of nasopharyngeal secretions may show RSV

## Management is largely supportive

- humidified oxygen is given via a head box and is typically recommended if the oxygen saturations are persistently < 92%
- nasogastric feeding may be needed if children cannot take enough fluid/feed by mouth
- suction is sometimes used for excessive upper airway secretions

## Bronchiolitis Obliterans

- It is the term used to describe **fibrous scarring** of the **small airway.**
- Histologically there is a **mural concentric narrowing** of the **lumina** of the **bronchioles**.
- It can present as severe respiratory insufficiency.
- Inflammation in the small distal airways leads to **obstructive** spirometry and without treatment this is relentlessly progressive. **Air trapping** can occur, which leads to increased lung volumes.
- It is seen following: toxic fume inhalation, mineral dust exposure, viral infection (**CMV**), legionella, and mycoplasma, **bone marrow transplantation, heart lung transplantation, early acute rejection and CMV infection, Rheumatoid arthritis**, SLE, side effect of **penicillamine**.
- Dry cough, dyspnoea, wheezes
- CXR: vary from normal to a reticular or reticulonodular pattern.
- Diagnosis: confirmed by **lung biopsy**.
- Progressive and relentless **fall in ($FEV_1$) the forced expiratory volume in one second** is the **most characteristic** of bronchiolitis obliterans.
- **Prognosis is poor**, Pts. rarely respond to **steroids**. Corticosteroids can induce a quick response and improvement in symptoms.

Bronchiolitis obliterans, with or without organising pneumonia, can be a **fatal** complication of **rheumatoid arthritis** (especially in **women** taking **penicillamine**).

Bronchiolitis obliterans has been seen as early as **3 months post-transplant**, like **heart** and **lung** or **BM** transplantation, and is responsible for **over 50% of deaths after the first year.**
**EX:** Pt underwent a heart-lung transplantation for pulmonary hypertension, then after 2 years develop SOB with obstructive pattern of PFTs >>>? **Bronchiolitis obliterans**

## Chronic cough

In epidemiological studies 16% of the UK population reported a persistent cough.

For the purposes of the BTS guidelines, cough is a forced expulsive manoeuvre against a closed glottis with a characteristic sound.

**Acute cough** is defined as one lasting **less than 3 weeks**.

**Chronic cough** is defined as one lasting **over 8 weeks**

There is a **grey area** between 3 to 8 weeks and this includes **post-viral coughs**.

| OTHER CAUSES OF CHRONIC COUGH |
|---|
| **Intrathoracic** |
| • Asthma<br>• Lung Cancer<br>• Tuberculosis<br>• Bronchiectasis<br>• Left Heart Failure<br>• Interstitial Lung Disease<br>• Cystic Fibrosis<br>• Idiopathic Cough |
| **Extrathoracic** |
| • Chronic Allergic Rhinitis<br>• Post Nasal Drip Syndrome (PNDS)<br>• Upper Airway Cough Syndrome (UACS)<br>• Gastroesophageal Reflux<br>• Medication (e.g. ACE Inhibitors) |

## Pulmonary Alveolar Proteinosis (PAP)

It is a rare diffuse lung disease in which the alveolar sacs become filled with protein-rich fluid that characteristically stain for **PAS**, a protein derived from surfactant.

It usually affects people aged between **20-60 years** who have **no previous** lung disease, **men** more frequently than women.

It can be primarily or secondary, the latter being related to infections with, for example, pneumocystitis Jirovecii or atypical mycobacteria, or to immunosuppressants, organic dusts and haematological malignancy.

It usually presents with **SOB** and **mild constitutional symptoms**.

**Diagnosis** based on **bronchial lavage** or **biopsy** with **PAS-positive stains** and increased presence of **surfactant proteins A and D.**

**HRCT** chest shows a classical picture of **dense infiltrates**, often referred to as **crazy paving.**

**Spirometry** shows a **restrictive pattern** with reduced lung capacity and reduced CO diffusion.

Most patients do not require ttt unless their SOB is disabling.

**Treatment:** is by **washing the alveoli out** with salt solution. This can be done with bronchoscopy or under general anaesthesia through the trachea. If both lungs need washing then they are done about 5 days apart. The number of washing depends on symptoms.

**Prognosis** is **good**.

## Ludwig's angina

It is rapidly spreading, life threating cellulitis of the **sublingual** and **submandibular** spaces that usually starts **in an infected lower mole**.

Airway obstruction and difficulty in breathing and talk may result as the infection spreads to the supraglottic tissues.

**Treatment:** IV antibiotic against streptococci and oral anaerobes and **take care of airway (call anaesthesiologist).**

## Alveolar microlithiasis

It is a rare condition, sometimes familial with **autosomal recessive** inheritance, with **female** predominance 2:1.

It is associated with deposition of **diffuse calcified microliths in alveolar space.**

Unfortunately progressive Ca deposition leads to **respiratory failure** with early age death.

CXR or CT: **fine micronodular calcification** predominantly at lung **base** and **hila**.
PFT shows **restrictive** pattern.

**No medical intervention** has proved successful, although lung transplantation has been used for some cases.

So much Ca deposition, the examined lungs at post-mortem were as so stiff as to require a saw to enable sectioning for examination.

# ARDS (acute respiratory distress syndrome)

It is a **severe** form of Acute Lung Injury (**ALI**) which describes a pulmonary syndrome characterised by **non-cardiogenic pulmonary oedema**.

It is caused by increased **permeability** of alveolar capillaries leading to fluid accumulation in alveoli (i.e., non-cardiogenic pulmonary oedema) >>> exudation of **high protein rich fluid** into the interstitium and alveoli.

It tends to be a **type 1** respiratory failure, rather than type 2.

## Clinical features are typically of an acute onset and severe:

- dyspnea
- elevated respiratory rate
- bilateral lung crackles
- low oxygen saturations

## The following are helpful in differentiating ARDS from other conditions, such as LVF:

- Normal heart size.
- Absent septal lines.
- Air bronchograms, and
- Peripheral distribution.

## Criteria (American-European Consensus Conference):

- **Acute onset**
- **Bilateral infiltrates on CXR**
- **PO2/FiO2 < 200 mmHg**
- **Non-cardiogenic** (pulmonary artery wedge pressure needed if doubt)
- **Low PCWP Pulmonary capillary wedge pressure (less than 18 mmHg).**

**CXR**:classically shows **bilateral peripheral** interstitial and alveolar infiltrates that become progressively more confluent but **spare** the costophrenic angles.

## A chest x-ray and arterial blood gases are the key investigations.

## Causes

- Infection: sepsis, pneumonia
- Massive blood transfusion
- Trauma
- Smoke inhalation injury
- **Pancreatitis**
- Cardio-pulmonary bypass

## Direct pulmonary causes of ARDS include:

- Inhalation of gastric contents (pH <2)
- Infective (pneumonia, **TB**)
- Pulmonary trauma
- **Near drowning**
- Toxic gas inhalation and
- Oxygen toxicity.

## Indirect causes include:

- Sepsis
- Non-thoracic trauma
- Uraemia
- Bowel infraction
- **Anaphylaxis** and
- **Burns**.
- **Post arrest**

ARDS **mortality** is generally **high (40%),** but is determined by the cause with aspiration pneumonia having a mortality rate of almost 80% when associated with ARDS.

Management is by mechanical ventilation with maximal ventilatory therapy (Her inspired oxygen **(FiO2) is 100%,** positive end expiratory pressure **(PEEP) is 15 cm$H_2O$** and **peak pressure** is **40** cm$H_2O$).

The mild high CO2 is a reflection of **permissive hypercapnia** to prevent over distension of the lungs with high tidal volumes.

IF but is still hypoxic (low SPO2) Treatment of these patients used to be extremely difficult, with no significant improvement in prognosis seen will any technique. However, trials demonstrated a significant increase in survival without significant disability with the use of extracorporeal membrane oxygenation (ECMO).
ECMO involves connecting a patient's circulation to an **external oxygenator** and **pump**, via a **catheter** placed in the **right** side of the heart. It requires the continuous **infusion** of **anticoagulant**, and as such **bleeding** is the most commonly associated complication. Infection and haemolysis are also a risk.

Prone positioning is widely accepted in clinical practice.

# Post-extubation stridor (PES)

PES is a **frequent** complication of intubation, occurring in **2-16%** of cases.

It is caused by laryngeal oedema that results from damage to the mucosa of the larynx.

Mucosal damage is caused by pressure and ischaemia resulting in an inflammatory response.

Laryngeal oedema, in severe cases, can lead to acute respiratory compromise necessitating emergency re-intubation.

## Risk factors for PES include:

- **Female** gender: may be due to the female mucous membrane being less resistant to trauma and thinner than that in men.
- Intubation **>36 hours.**
- **Excessive** cuff pressure.
- **Large** tube size.
- Tracheal **infection**.

**NB: Age and asthma are not known risk factors for PES.**

# Gastroenterology & Hepatology

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# General

## Gastrointestinal enzymes Acid secretion

**Amylase** is present in saliva and pancreatic secretions. It **breaks starch down into sugar.**

The following brush border enzymes are involved in the breakdown of carbohydrates:

- **Maltase:** cleaves disaccharide maltose to glucose + glucose
- **Sucrase:** cleaves sucrose to glucose and fructose
- **Lactase:** cleaves disaccharide lactose to glucose + galactose

**Brush border enzymes:**

- **Maltase**: glucose + glucose
- **Sucrase**: glucose + fructose
- **Lactase**: glucose + galactose

## Gastrointestinal hormones

**Below is a brief summary of the major hormones**

| | Source | Stimulus | Actions |
|---|---|---|---|
| **Gastrin** | **G cells in antrum of the stomach** | **Distension** of stomach, swallowing, Vagus nerves (mediated by gastrin-releasing peptide), luminal peptides/amino acids. Ach, histamine **Inhibited by:** Low antral pH, Somatostatin. Prostaglandin | **Increase HCL, pepsinogen and IF secretion, increases gastric motility, stimulates parietal cell maturation** |

| | | | |
|---|---|---|---|
| **CCK** | **I cells in upper small intestine** | Partially digested proteins and triglycerides | **Stimulates contraction of the gallbladder.** Increases secretion of enzyme-rich fluid from pancreas, **contraction of gallbladder** and relaxation of sphincter of Oddi, decreases gastric emptying, trophic effect on pancreatic acinar cells, induces satiety |
| **Secretin** | **S cells in upper small intestine** | Acidic chyme, fatty acids | **Increases secretion of $HCO_3$ -rich fluid from pancreas and liver. Decreases gastric acid secretion.** Trophic effect on pancreatic acinar cells. |
| **VIP** | Small intestine, pancreas | Neural | It is a **vasodilator** and also regulates **smooth muscle activity, epithelial cell secretion and gastrointestinal blood flow.** Stimulates secretion by pancreas and intestines, inhibits acid secretion |
| **Somatostatin** | **D cells in the pancreas & stomach** | Fat, bile salts and glucose in the intestinal lumen | **Inhibits all gastrointestinal endocrine secretions:** Decreases acid and pepsin secretion, decreases gastrin secretion, decreases pancreatic enzyme secretion, decreases insulin and glucagon secretion inhibits trophic effects of gastrin, stimulates gastric mucous production |

Brunner's glands which secrete alkaline mucus are found in the duodenum

Q: Which hormone is most responsible for the secretion of bicarbonate in the upper gastrointestinal tract? Secretin

## Intrinsic factor

- Intrinsic factor is a glucoprotein secreted from the **parietal cells** which are **found in the fundus of the stomach** in response to gastrin, food or histamine.
- intrinsic factor transport vitamin B12 across the mucosal wall.
- When **the vitamin B12 bound to intrinsic factor** reaches the **terminal ileum**, it binds to receptors on the surface of the mucosal cells **and is able to cross the membrane and enter the cytoplasm.**
- **The intrinsic factor is then replaced by transcobalamin II which transports the B12 out of the cell and into the bloodstream.**

## Pancreatic cells

- Islet **A** cells produce **glucagon**
- Islet **β** cells produce: **insulin** and **amylin**, as well as **C peptide**, **pro-insulin** and **GABA**.
- Islet **D** cells produce **somatostatin**
- Islet **F** cells produce **pancreatic polypeptide**

Gastric **chief** cells produce: **pepsinogen**
Gastric **parietal** cells produce **HCL** and **intrinsic factor (IF)**.

## Gastrointestinal cause of clubbing

- Hepatic cirrhosis
- Coeliac disease
- Crohn's disease
- Ulcerative colitis
- Whipple's disease
- GI lymphoma

**Ilio-caecal TB >> no clupping**

## Hiccup

caused by frequent or rhythmic clonic contraction of the diaphragm.
When prolonged, other causes should be considered including:

- CNS disease - posterior fossa tumour, brain injury, encephalitis
- Phrenic nerve or diaphragm irritation - tumour, pleurisy, pneumonia, intrathoracic adenopathy, pericarditis, gastro-oesophageal reflux, oesophagitis
- Systemic causes include alcohol intoxication and uraemia.
- Other causes include foreign body or insect in the ear.
- In infants it may be associated with apnoea or hyperventilation.

### Treatment

- Folk remedies include aerophagia, breath holding, pharyngeal stimulation, distraction.
- Haloperidol, metaclopramide and several anaesthetic agents are also said to work.

## Pharyngeal pouch (Oesophageal diverticula)

A pharyngeal pouch is a posteromedial diverticulum through Killian's dehiscence.
Killian's dehiscence is a triangular area in the wall of the pharynx between the thyropharyngeus and cricopharyngeus muscles.
It is more common in **older** patients and is 5 times more common in **men.**

### Associations

- they may be related to **poor** relaxation of the upper esophageal sphincter.
- association with gastro-esophageal reflux disease has been noted.

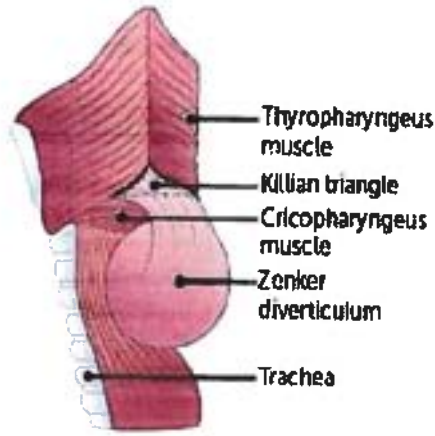
### Features:

- **Dysphagia to solids and liquids**
- Regurgitation of **rotten undigested** food
- **Halitosis**
- **Nocturnal** chronic cough
- Aspiration >> pneumonia
- Neck swelling which gurgles on palpation

### Diagnosis:

- **Barium swallow.**
- Detected best by using **lateral X-ray shows** a contrast-filled pouch **protruding dorsally from the hypopharynx at the level of C5/C6**

- Upper gastrointestinal **endoscopy** is **risky**,
  - since the pouches are thin-walled and easy to **perforate**
  - **this is the reason why a barium swallow may be the preferable first-line investigation in elderly patients with dysphagia.**
- Upper endoscopy under direct vision should be performed to exclude malignancy




## Management:

- Surgical, with either an open or endoscopic approach.
- Either diverticulectomy for larger lesions, or
- Dohlman's procedure for smaller pouches

(traction diverticula and epiphrenic diverticula) usually do not require treatment

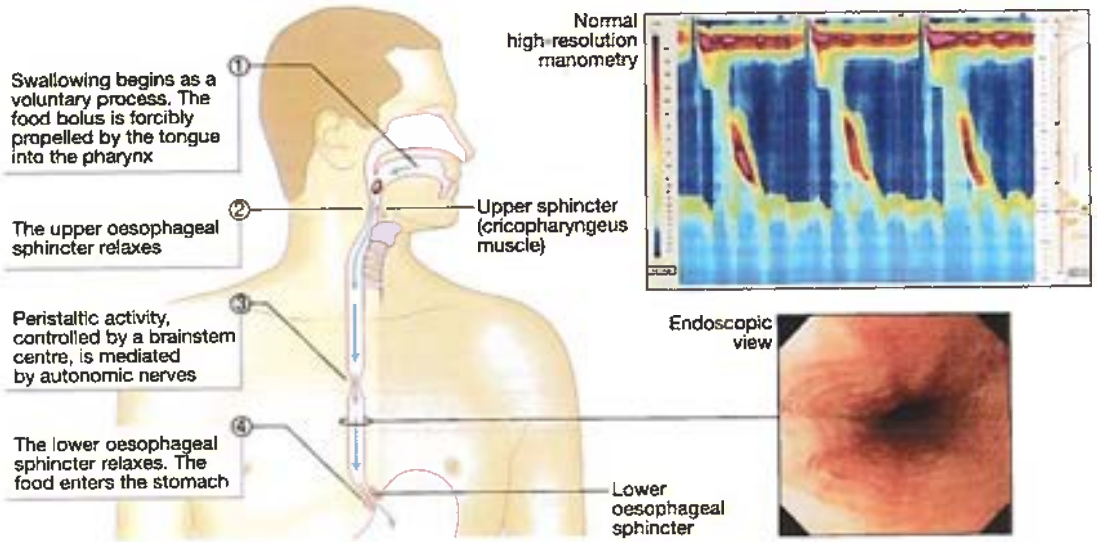
Still image taken from a barium swallow with fluoroscopy. During swallowing an outpouching of the posterior hypopharyngeal wall is visualised at the level C5-C6, right above the upper esophageal sphincter.

# Esophagus

## Esophageal disorders

**The table below lists a small group of less common oesophageal disorders.**

| Disorder | Notes |
|---|---|
| Plummer-Vinson syndrome | **Triad of:**<br>• dysphagia (secondary to oesophageal webs)<br>• glossitis<br>• iron-deficiency anaemia<br>Treatment includes iron supplementation and dilation of the webs |
| **Mallory-Weiss syndrome** | Severe vomiting → painful mucosal lacerations at the gastroesophageal junction resulting in haematemesis. Common in alcoholics |
| **Boerhaave syndrome** | Severe vomiting → oesophageal rupture |


Swallowing begins as a voluntary process. The food bolus is forcibly propelled by the tongue into the pharynx
The upper oesophageal sphincter relaxes
Peristaltic activity, controlled by a brainstem centre, is mediated by autonomic nerves
The lower oesophageal sphincter relaxes. The food enters the stomach
Upper sphincter (cricopharyngeus muscle)
Lower oesophageal sphincter
Normal high-resolution manometry
Endoscopic view

# Abdominal pain (in MRCP)

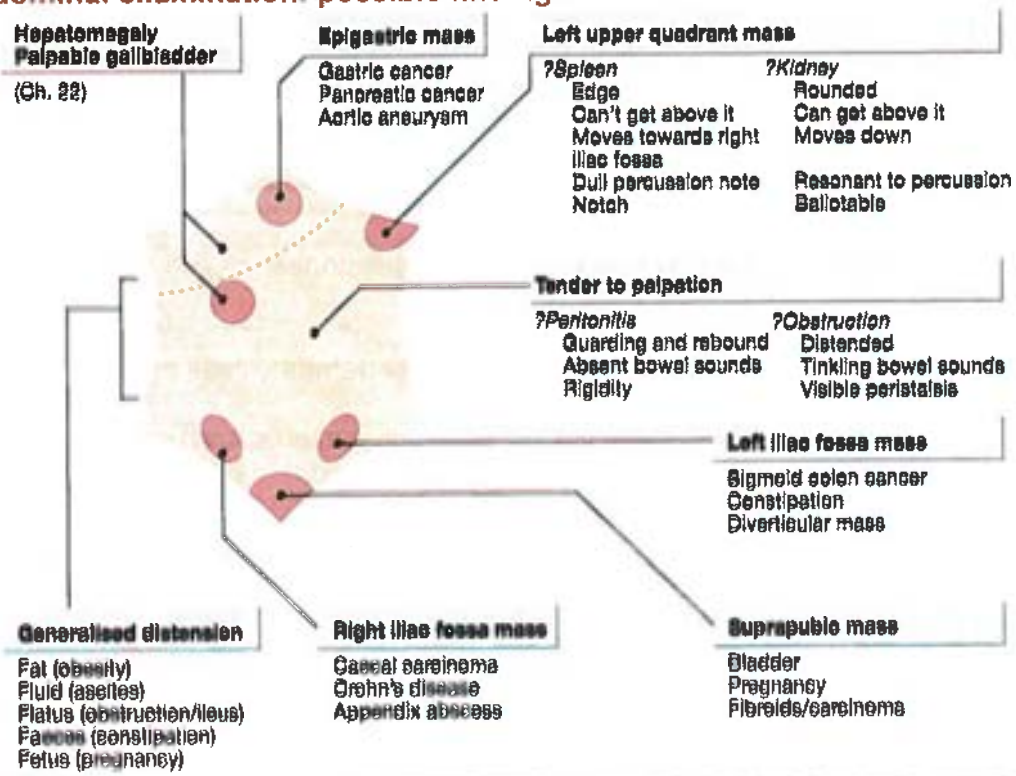
The table below gives characteristic exam question features for conditions causing abdominal pain. Unusual and 'medical' causes of abdominal pain should also be remembered:

- **acute coronary syndrome.**
- **diabetic ketoacidosis.**
- **pneumonia.**
- **acute intermittent porphyria**
- **lead poisoning.**
- **Addison's disease.**
- **Familial Mediterranean fever.**
- **HSP.**

| Condition | Characteristic exam feature |
|---|---|
| **Peptic ulcer disease** | **Duodenal ulcers:** more common than **gastric ulcers,** epigastric pain relieved by eating<br>Gastric ulcers: epigastric pain worsened by eating<br>Features of upper gastrointestinal haemorrhage may be seen (haematemesis, melena etc) |
| **Appendicitis** | Pain initial in the central abdomen before localising to the right iliac fossa<br>Anorexia is common<br>Tachycardia, low-grade pyrexia, tenderness in RIF<br>Rovsing's sign: more pain in RIF than LIF when palpating LIF |
| **Acute pancreatitis** | Usually due to alcohol or gallstones<br>Severe epigastric pain<br>Vomiting is common<br>Examination may reveal tenderness, ileus and low-grade fever<br>Periumbilical discolouration (Cullen's sign) and flank discolouration (Grey-Turner's sign) is described but rare |
| **Biliary colic** | Pain in the RUQ radiating to the back and interscapular region, may be following a fatty meal. Slight misnomer as the pain may persist for hours<br>Obstructive jaundice may cause pale stools and dark urine<br>It is sometimes taught that patients are female, forties, fat and fair although this is obviously a generalisation |

| Condition | Characteristic exam feature |
|---|---|
| Acute cholecystitis | History of gallstones symptoms (see above)<br>Continuous RUQ pain<br>Fever, raised inflammatory markers and white cells<br>Murphy's sign positive (arrest of inspiration on palpation of the RUQ) |
| Diverticulitis | Colicky pain typically in the LLQ<br>Fever, raised inflammatory markers and white cells |
| Abdominal aortic aneurysm | Severe central abdominal pain radiating to the back<br>Presentation may be catastrophic (e.g. Sudden collapse) or sub-acute (persistent severe central abdominal pain with developing shock)<br>Patients may have a history of cardiovascular disease |
| Intestinal obstruction | History of malignancy/previous operations<br>Vomiting<br>Not opened bowels recently<br>'Tinkling' bowel sounds |

## Abdominal examination: possible findings



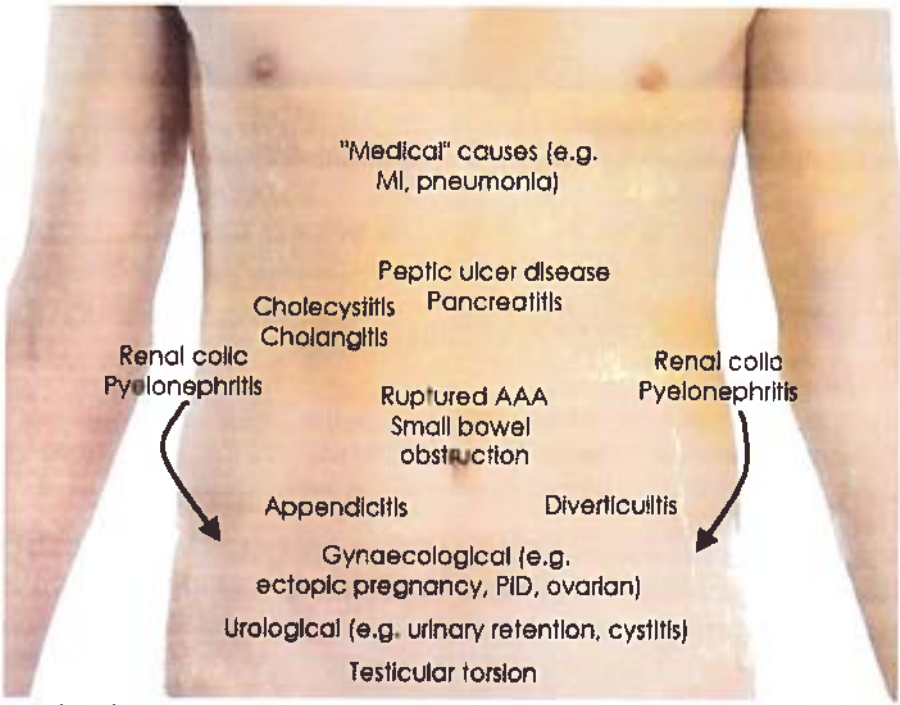
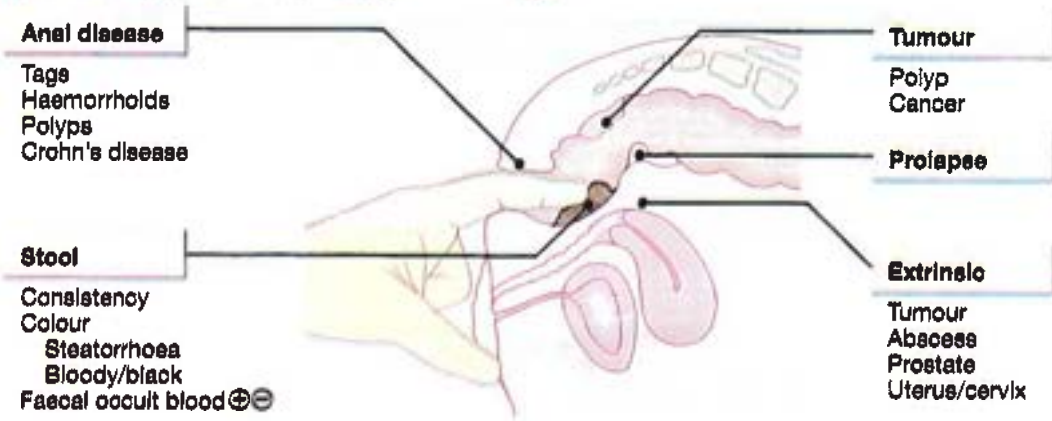



Diagram showing stereotypical areas where particular conditions present. The diagram is not exhaustive and only lists the more common conditions seen in clinical practice. Note how pain from renal causes such as renal/ureteric colic and pyelonephritis may radiate and move from the loins towards the suprapubic area.

## Rectal examination: common findings



# Achalasia

- Failure of oesophageal peristalsis and of relaxation of lower oesophageal sphincter (LOS) due to degenerative loss of ganglia from Auerbach's plexus i.e., LOS contracted, oesophagus above dilated.
- Achalasia can present at any age but typically presents in middle-age most often in the 3rd to 5th decades.
- It is equally common in men and women.
- It affects an estimated 10 in 10,000 people.

## Clinical features:

- Symptoms usually develop **years** before the patient presents
- Typically, variation in severity of symptoms
- Dysphagia **of BOTH liquids and solids(more to solids)**
- Heartburn.
- **Vague chest discomfort** is common
- Regurgitation of food - may lead to cough, aspiration pneumonia (30% have a **nocturnal cough** due to aspiration of oesophageal contents).
- Malignant change in small number of patients

A longstanding history of dysphagia to both solids and liquids suggests a functional rather than mechanical cause for the dysphagia.

## Investigations:

- **Oesophageal manometry:** excessive LOS tone which doesn't relax on swallowing - considered most important definitive diagnostic test.
  - **Will show:**
    - excessive LOS tone which doesn't relax on swallowing
    - Lack of peristalsis in the lower two-thirds of the esophagus
- **Barium swallow** shows grossly expanded oesophagus, typical bird's peak appearance, fluid level.
- **Upper endoscopy**
  - to rule out pseudoachalsia
  - Usually, normal
  - May show retained food in oesophagus or increased resistance of LES during passage with endoscope
- **CXR:** Will show:
  - **wide mediastinum,**
    - Widened mediastinum is where the mediastinum has a width greater than **6 cm** on an upright **PA** chest X-ray or **8 cm** on supine **AP** chest film.
  - **fluid level**

The gold standard test for **achalasia** is >>>> **oesophageal manometry**

## Treatment:

- **Heller cardiomyotomy:** good to excellent symptom response in 82% of patients and show symptom response rates of 84-100%.
- **Balloon dilation:** is usually attempted before laparoscopic surgical myotomy.
- Intra-sphincteric injection of **botulinum toxin**: its effects are short lived (typically <6 months) and use is generally recommended to be restricted to the frail or elderly in whom more aggressive therapy poses high risk.
- drug therapy (e.g. **nitrates, calcium channel blockers**) has a role but is limited by side-effects

This film demonstrates the classical 'bird's beak' appearance of the lower oesophagus that is seen in achalasia. An air-fluid level is also seen due to a lack of peristalsis

Mediastinal widening secondary to achalasia. An air-fluid level can sometimes be seen on CXR but it is not visible on this film

Barium swallow - grossly dilated filled oesophagus with a tight stricture at the gastroesophageal junction resulting in a 'bird's beak' appearance. Tertiary contractions give rise to a corkscrew appearance of the oesophagus

**The most appropriate initial investigation of a high dysphagia is a barium swallow, which identifies the site of pathology and forewarns of pitfalls such as a pharyngeal pouch, which if unidentified can increase the risk of perforation at endoscopy.**

## Diffuse esophageal spasm

### Features

- dysphagia
- chest pain

### Diagnosis

- barium **swallow**
  demonstrates a 'corkscrew appearance'
- Manometry reveals:
  - prolonged, repetitive and high amplitude contractions.
  - The lower oesophageal sphincter pressure is increased and there is incomplete relaxation of the sphincter.

### Differential diagnosis manometry findings:

- absence of peristalsis in the body of the oesophagus + high lower oesophageal sphincter → **Achalasia**
- normal contractions in the body of the oesophagus + high lower oesophageal sphincter pressure
  - **hypertensive lower oesophageal sphincter**
- high amplitude contractions in the body of the oesophagus + high lower oesophageal sphincter pressure
  - **Diffuse oesophageal spasm**

# Dysphagia

The table below gives characteristic exam question features for conditions causing dysphagia

| Causes | Notes |
|---|---|
| **Oesophageal cancer** | **Dysphagia may be associated with weight loss, anorexia or vomiting during eating**<br>**Past history may include Barrett's oesophagus, GORD, excessive smoking or alcohol use** |
| **Oesophagitis** | May be history of heartburn<br>Odynophagia but no weight loss and systemically well |
| **Oesophageal candidiasis** | There may be a history of HIV or other risk factors such as steroid inhaler use<br>Treatment >> oral or IV therapy (usually with fluconazole or itraconazole for at least 14-21 days). |
| **Achalasia** | Dysphagia of both liquids and solids from the start<br>Heartburn<br>Regurgitation of food - may lead to cough, aspiration pneumonia etc |
| **Pharyngeal pouch** | More common in older men<br>Represents a posteromedial herniation between thyropharyngeus and cricopharyngeus muscles<br>Usually not seen but if large then a midline lump in the neck that gurgles on palpation<br>Typical symptoms are dysphagia, regurgitation, aspiration and chronic cough. Halitosis may occasionally be seen |
| **Systemic sclerosis** | Other features of CREST syndrome may be present, namely Calcinosis, Raynaud's phenomenon, oEsophageal dysmotility, Sclerodactyly, Telangiectasia<br>As well as oesophageal dysmotility the lower oesophageal sphincter (LES) pressure is decreased. This contrasts to achalasia where the LES pressure is increased |
| **Myasthenia gravis** | Other symptoms may include extraocular muscle weakness or ptosis<br>Dysphagia with liquids as well as solids. |

| Causes | Notes |
|---|---|
| **Oesophageal cancer** | **Dysphagia may be associated with weight loss, anorexia or vomiting during eating**<br>**Past history may include Barrett's oesophagus, GORD, excessive smoking or alcohol use** |
| **Globus hystericus** | May be history of anxiety<br>Symptoms are often intermittent and relieved by swallowing<br>Usually painless - the presence of pain should warrant further investigation for organic causes |

## Causes of dysphagia - by classification

As with many conditions, it's often useful to think about causes of a symptom in a structured way:

| Classification | Examples |
|---|---|
| **Extrinsic** | • Mediastinal masses<br>• Cervical spondylosis |
| **Oesophageal wall** | • Achalasia<br>• Diffuse oesophageal spasm<br>• Hypertensive lower oesophageal sphincter |
| **Intrinsic** | • Tumours<br>• Strictures<br>• Oesophageal web<br>• Schatzki rings |
| **Neurological** | • CVA<br>• Parkinson's disease<br>• Multiple Sclerosis<br>• Brainstem pathology<br>• Myasthenia Gravis |

## Investigation

- All patients require an upper GI endoscopy unless there are compelling reasons for this not to be performed.
- Motility disorders may be best appreciated by undertaking fluoroscopic swallowing studies.
- A full blood count should be performed.
- Ambulatory oesophageal pH and manometry studies will be required to evaluate conditions such as achalasia and patients with GORD being considered for fundoplication surgery.

# Gastro-esophageal reflux disease (GORD)

## Overview:

- **Poor correlation** between symptoms and endoscopy appearance.
- It occurs during **transient relaxation** of the lower oesophageal sphincter (LES).

## Indications for upper GI endoscopy:

- Age > 55 years
- Symptoms > 4 weeks or persistent symptoms despite treatment
- Dysphagia
- Relapsing symptoms
- Weight loss

If endoscopy is negative >>> consider **24-hr oesophageal pH monitoring** (the **gold** standard test for diagnosis of GERD).

## Treatment

- **Monitoring of pH is not a good guide to therapy but symptomatic improvement is a good guide to the efficacy of therapy.**
- **Laparoscopic fundoplication** is the treatment of choice for patients with GORD **refractory** to or intolerant of proton pump inhibitor therapy.
- The patient should have had an **endoscopy within the 6 months prior** to surgery to exclude any unsuspected pathology such as Barrett's oesophagus or adenocarcinoma.
- An **oesophageal transit study** is indicated to **rule out a primary motor** disorder (for example, achalasia, scleroderma) when suspected and to rule out aperistalsis, which may result in postoperative dysphagia after some forms of fundoplication.

Pt with severe GERD, so the most useful test in assessing the role of surgery is >>> **Oesophageal motility and pH study**

- Offer people a full-dose PPI for 8 weeks to heal severe esophagitis, taking into account the person's preference and clinical circumstances (for example, underlying health conditions and possible interactions with other drugs).
- Offer a full-dose PPI long-term as maintenance treatment for people with severe esophagitis, taking into account the person's preference and clinical circumstances.
- lifestyle changes
  - Small portions;
  - avoid eating (< 3 hours) before bedtime.
  - Avoid foods with high fat content

- **Avoid**: nicotine, alcohol, coffee and certain drugs (e.g., calcium channel blockers, diazepam)

## GORD management

- **1st line** - lifestyle changes
  - don't lie down after eating
  - avoid spicy foods
  - eat small servings
- **2nd line >>** proton pump inhibitors (omeprazole, lansoprazole)
- **3rd line >>** H2 receptor antagonists(cimetidine, ranitidine)
- **4th line >>** Surgical Nissen fundoplication or hiatal hernia repair

## Complications

- metaplasia of the lower esophagus, which is the first stage of Barrett esophagus.
- **Esophageal strictures** occur in 10%
  - Two types of rings (**Schatzki rings**):
    - ➢ muscular ring, or A ring:
      - located approximately 2 cm above the gastroesophageal junction.
      - rare
    - ➢ mucosal ring, or B ring,
      - **most common**
      - located at the squamo-columnar junction.
  - mechanical cause of dysphagia
    - ➢ characterized by **progressive symptoms**. Patients often first notice difficulty swallowing solid foods, and this then progresses to softer foods, and then fluids.
  - most patients respond well to dilatation therapy.
- adenocarcinoma of the lower esophagus.

# Barrett's oesophagus

## NICE Guidelines 2019

- Chronic GORD changes stratified squamous epithelium into columnar epithelium at lower end of esophagus and can turn to adenocarcinoma.
- It occurs in 1-4% of patients with GORD, the rate of transformation to adenocarcinoma is 0.2-2% per year. –

**NB:** Correlation between heart burn & esophagitis is poor as some patients have mild esophagitis but sever heart burn and vice versa.

- It may present with iron deficiency or hematemesis.
- 20% pf patients admitted to CCU are due to esophageal Pain.
- Reflux means PH< 4.0 at lower oesophagus.

**Treatment:** 50% of patients Can be cured by: - weight loss, PPI, raise head, decrease coffee and quit smoking. - Alginate containing antacids 10ml TID, dopamine antagonists, H2 receptors blockers, and PPI.

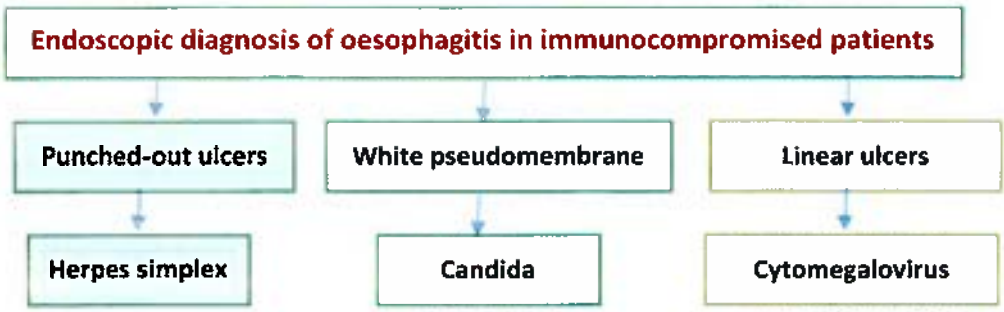
## Endoluminal Gastroplication and Surgery

**Endoscopic screening of Barrett's esophagus every 2 years but:**
If higher grade dysplasia **plus**.

- **no visual lesion** (only by BIOPSY) treated by High dose PPI & repeat biopsies EVERY 3 months with endoscopy.
- **visual nodules or ulcers:**
  a) Endoscopic mucosal or submucosal resection or Radiofrequency ablation)
  b) Radio Frequency ablation: return mucosa to squamous epithelium

## Oesophagitis in immunosuppressive patients

**HIV patient presented with painfull swallowing difficulty, an upper GI endoscopy shows ulcerative oesophagitis, what is the most likely diagnosis?**



### Treatment

- Candida spp
  - Nonpregnant patients, we suggest initial therapy with fluconazole
  - Pregnant patients →amphotericin Bis the treatment of choice during the first trimester since oral azoles are teratogenic.
- Herpes simplex virus (HSV)→ oral or iV acyclovir
- Cytomegalovirus →ganciclovir or valganciclovir

TREATMENT MUST BE FOR AT LEAST 14 DAYS TO AVOID RECURRANCE

## Eosinophilic oesophagitis (EOE)

### Causes

- unknown,
- **allergies**
  - At least **50% of children with EoE have allergies**, including food allergies, allergic rhinitis (hay fever) and asthma.

### Features

- **episodic oesophageal spasm and intermittent dysphagia**

### Diagnosis

- by endoscopy and **biopsy** → presence of **eosinophils**

### Treatment

- **Responds to "swallowed" steroid**

## Acute upper gastrointestinal bleeding

Acute upper gastrointestinal (GI) bleeding is a common and important presentation. It may be caused by a wide variety of conditions but is most commonly due to either esophageal varices or peptic ulcer disease.

### Clinical features

- **haematemesis**
  - the most common presenting feature
  - often bright red but may sometimes be described as 'coffee gound'
- **melena**
  - the passage of altered blood per rectum
  - typically black and 'tarry'
- **a raised urea may be seen due to the 'protein meal' of the blood**
- features associated with a particular diagnosis e,g,
  - oesophageal varices: stigmata of chronic liver disease
  - peptic ulcer disease: abdominal pain

## Differential diagnosis

### Oesophageal causes

| Cause | Presenting features |
|---|---|
| **Oesophageal varices** | Usually a large volume of fresh blood. Swallowed blood may cause melena. Often associated with haemodynamic compromise. May stop spontaneously but re-bleeds are common until appropriately managed. |
| **Oesophagitis** | Small volume of fresh blood, often streaking vomit. Malena rare. Often ceases spontaneously. Usually history of antecedent GORD type symptoms. |
| **Cancer** | Usually small volume of blood, except as a preterminal event with erosion of major vessels. Often associated symptoms of dysphagia and constitutional symptoms such as weight loss. May be recurrent until malignancy managed. |
| **Mallory Weiss tear** | Typically brisk small to moderate volume of bright red blood following a bout of repeated vomiting. Malena rare. Usually ceases spontaneously. |

### Gastric causes

| Cause | Presenting features |
|---|---|
| **Gastric ulcer** | Small low volume bleeds are more common so would tend to present as iron deficiency anaemia. Erosion into a significant vessel may produce considerable haemorrhage and haematemesis. |
| **Gastric cancer** | May be frank haematemesis or altered blood mixed with vomit. Usually prodromal features of dyspepsia and may have constitutional symptoms. Amount of bleeding variable but erosion of major vessel may produce considerable haemorrhage. |
| **Dieulafoy lesion** | Often no prodromal features prior to haematemesis and melena, but this arteriovenous malformation may produce quite a considerable haemorrhage and may be difficult to detect endoscopically |
| **Diffuse erosive gastritis** | Usually haematemesis and epigastric discomfort. Usually there is an underlying cause such as recent NSAID usage. Large volume haemorrhage may occur with considerable haemodynamic compromise |

### Duodenual causes

| Cause | Presenting features |
|---|---|
| **Duodenal ulcer** | These are usually posteriorly sited and may erode the gastroduodenal artery.<br>However, ulcers at any site in the duodenum may present with haematemesis, melena and epigastric discomfort.<br>The pain of a duodenal ulcer is slightly different to that of gastric ulcers and often occurs several hours after eating.<br>Periampullary tumours may bleed but these are rare. |
| **Aorto-enteric fistula** | In patients with previous abdominal aortic aneurysm surgery aorto-enteric fistulation remains a rare but important cause of major haemorrhage associated with high mortality. |

## Management

NICE published guidelines on the management of acute upper gastrointestinal bleeding which is most commonly due to either peptic ulcer disease or oesophageal varices. Some of the key points are detailed below.

### Risk assessment

- the Glasgow-**Blatchford score** at first assessment
  - helps clinicians decide whether patient patients can be managed as outpatients or not
- **the Rockall score** is used after endoscopy
  - provides a percentage risk of rebleeding and mortality
  - includes age, features of shock, co-morbidities, aetiology of bleeding and endoscopic stigmata of recent haemorrhage

**Blatchford score**

| Admission risk marker | Score |
|---|---|
| **Urea (mmol/L)**<br><br>**(High urea levels in upper GI bleeds are due to the 'protein meal' of blood)** | 6·5 - 8 = 2<br>8 - 10 = 3<br>10 - 25 = 4<br>> 25 = 6 |
| **Haemoglobin (g/L)** | **Men**<br>• 12 - 13 = 1<br>• 10 - 12 = 3<br>• < 10 = 6<br>**Women**<br>• 10 - 12 = 1<br>• < 10 = 6 |
| **Systolic blood pressure (mmHg)** | 100 - 109 = 1<br>90 - 99 = 2<br>< 90 = 3 |

| Admission risk marker | Score |
|---|---|
| **Other markers** | Pulse >=100/min = 1<br>Presentation with melaena = 1<br>Presentation with syncope = 2<br>Hepatic disease = 2<br>Cardiac failure = 2 |

Patients with a Blatchford score of 0 may be considered for early discharge.

## The Rockall scoring system

- Used to:
  - determine the prognosis of upper GIT bleeds.
  - assess severity of GIT bleeds and / or to triage patients for emergency endoscopy.
- Consists of **5** categories:

| | Score 0 | Score 1 | Score 2 | Score 3 |
|---|---|---|---|---|
| **Age** | <60 | 60-79 | >80 | - |
| **Shock** | No shock | Pulse >100 | SBP <100 mmHg | - |
| **Co-morbidity** | Nil major | | CCF, **IHD**, major morbidity | **Renal** or **liver** failure, **metastatic** cancer |
| **Diagnosis** | Mallory-Weiss tear | All other diagnoses | GI malignancy | - |
| **Evidence of bleeding** | **None** | - | Blood, adherent clot, spurting vessel | - |

Increasing scores are strongly correlated with increasing risk of mortality, correlation with risk of re-bleeding is also present but not as strong.
Each category is scored between 0 and 2 points, with the exception of co-morbidities which has a maximum score of 3.

The weighting of points corresponds to the additional risk of death that parameter confers.

**Renal failure**, **liver failure** and **metastatic cancer** carry the **highest** points, and thus confer the highest risk of death, of any of the other parameters included in the scoring system.

**The Baylor bleeding score** attaches a score to pre- and post-endoscopic features.

### Resuscitation

- ABC, wide-bore intravenous access * 2
- platelet transfusion if actively bleeding platelet count of less than 50 x 10*9/litre
- fresh frozen plasma to patients who have either a fibrinogen level of less than 1 g/litre, or a prothrombin time (international normalised ratio) or activated partial thromboplastin time greater than 1.5 times normal
- prothrombin complex concentrate to patients who are taking warfarin and actively bleeding

### Endoscopy

- should be offered immediately after resuscitation in patients with a severe bleeding
- all patients should have endoscopy within 24 hours
- **He may have alcohol dependency and therefore should be prescribed Pabrinex whilst waiting for endoscopy. .**
  - **the most appropriate intervention to prevent further bleeding → IV omeprazole**
    - reduction in risk of recurrent bleeding of over 50%,
    - reduction in need for surgical intervention of approximately 40%.
- if further bleeding then options include repeat endoscopy, interventional radiology and surgery

### Management of variceal bleeding

- terlipressin and prophylactic antibiotics should be given to patients at presentation (i.e., before endoscopy) Terlipressin dose is 2 mg IV stat followed by 1- 2 mg every four to six hours for 72 hours or until the bleeding stops. It is contraindicated in patients with known vascular disease or an ischaemic ECG.
- band ligation should be used for oesophageal varices and injections of N-butyl-2-cyanoacrylate for patients with gastric varices
- transjugular intrahepatic portosystemic shunts (TIPS) should be offered if bleeding from varices is not controlled with the above measures

- In severe hematemesis with the presence of large bleeding duodenal ulcer and unable to reach it by scope >>> **Angiography with selective embolization**.

- **EX**: Pt with recurrent attacks of melena and now he is free, OGD and colonoscopy both are unremarkable >>> So, **Meckel's Scan** or **capsule enteroscopy**.

Antibiotic prophylaxis reduces **mortality** in cirrhotic patients with GIT bleeding

**Terlipressin** - method of action >>> constriction of the splanchnic vessels

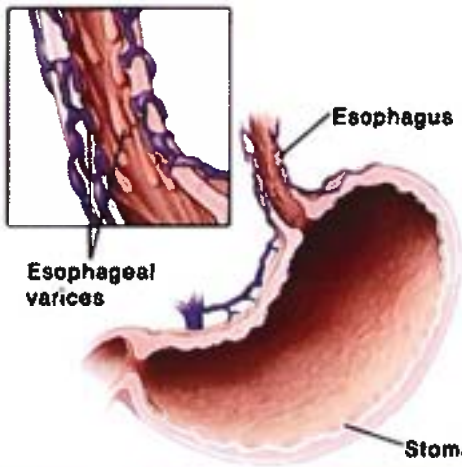
## Prophylaxis of variceal haemorrhage:

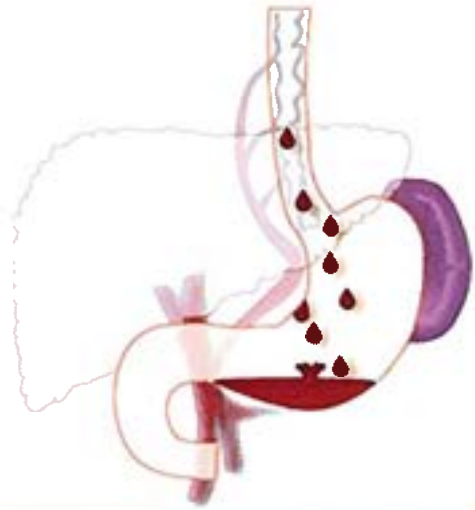
### Propranolol

- reduced rebleeding and mortality compared to placebo provided that pulse rate reduced by 25% than before start of treatment.

### Endoscopic variceal band ligation (EVL)

- is superior to endoscopic sclerotherapy.
- It should be performed at two-weekly intervals until all varices have been eradicated.
- **Proton pump inhibitor cover** is given to prevent EVL-induced **ulceration.**



| Disorder | Notes |
|---|---|
| Plummer-Vinson syndrome | **Triad of:**<br>• dysphagia (secondary to oesophageal webs)<br>• glossitis<br>• iron-deficiency anaemia<br>Treatment includes iron supplementation and dilation of the webs |
| Mallory-Weiss syndrome | Severe vomiting → painful mucousal lacerations at the gastroesophageal junction resulting in haematemesis. Common in alcoholics |

## Esophageal Rupture & Tears (Boerhaave's syndrome)

**(Boerhaave's syndrome).**

**Mackler's triad** (**vomiting**, **chest pain** and **surgical emphysema**) is classical but absent in almost half the cases.

**EX:** Severe sudden onset chest pain during a paroxysm of vomiting and pleural effusion >>> raise the suspicion of oesophageal rupture.

The chest x ray may confirm the surgical emphysema.

A **gastrografin swallow** is **diagnostic** and identifies the site and extent of rupture. This may determine the most appropriate treatment. However, it has a false negative rate of at least 10%.

A **CT scan** should be done if a gastrografin swallow is not possible or negative. as of oedema and haemorrhage a CT scan **may not** identify the site of the perforation.

**Lateral neck x rays** may be useful in the **early** stages where the diagnosis is uncertain and surgical emphysema is **not** seen on a plain CXR.

**Oesophagoscopy** has a role in if the gastrograffin swallow is negative.

## Oesophageal cancer

Until recent times oesophageal cancer was most commonly due to a **squamous** cell carcinoma which found mainly in the **upper** and **middle** third of the oesophagus but the incidence of **adenocarcinoma** is rising rapidly.

**Adenocarcinoma** is now the **most common** type of oesophageal cancer and is more likely to develop in patients with a history of gastro-oesophageal reflux disease (**GORD**) or **Barrett's**.

The majority of this tumours are in the **lower third** of the oesophagus.

whereas squamous cell tumours are most commonly found in the upper two-thirds of the oesophagus.

| | Adenocarcinoma | Squamous cell cancer |
|---|---|---|
| **Epidemiology** | Most common type in the UK/US | Most common type in the developing world |
| **Location** | Lower third - near the gastroesophageal junction | Upper two-thirds of the oesophagus |
| **Risk factors** | • **GORD**<br>• **Barrett's oesophagus**<br>• smoking<br>• achalasia<br>• obesity | • smoking<br>• alcohol<br>• achalasia<br>• Plummer-Vinson syndrome<br>• diets rich in nitrosamines |

## Features

- dysphagia: the most common presenting symptom
  - **Initially worse on solids and then later to include liquids**
- anorexia and weight loss
- vomiting
- other possible features include: odynophagia, hoarseness, melaena, cough
- Dermatological manifestations : Tylosis

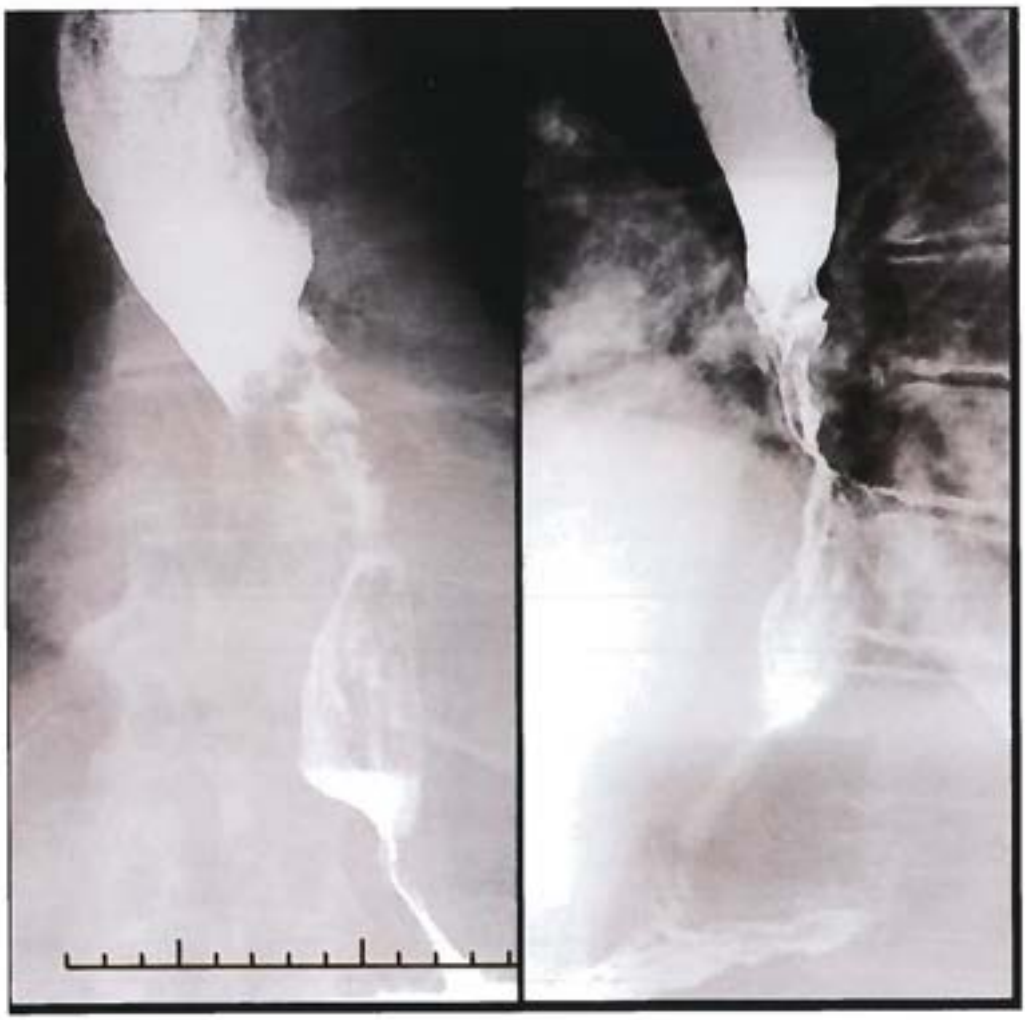
## Diagnosis

- Upper GI endoscopy with biopsy is used for diagnosis
- **Endoscopic ultrasound** is the preferred method for locoregional staging
- CT scanning of the chest, abdomen and pelvis is used for initial staging
  - FDG-PET CT may be used for detecting occult metastases if metastases are not seen on the initial staging CT scans.
  - Laparoscopy is sometimes performed to detect occult peritoneal disease

## Treatment

- Operable disease is best managed by surgical resection - the most common procedure is an Ivor-Lewis type oesophagectomy
  - This procedure involves the mobilisation of the stomach and division of the esophageal hiatus.
  - The abdomen is closed and a right sided thoracotomy performed.
  - The stomach is brought into the chest and the esophagus mobilised further.
  - An intrathoracic oesophagogastric anastomosis is constructed.

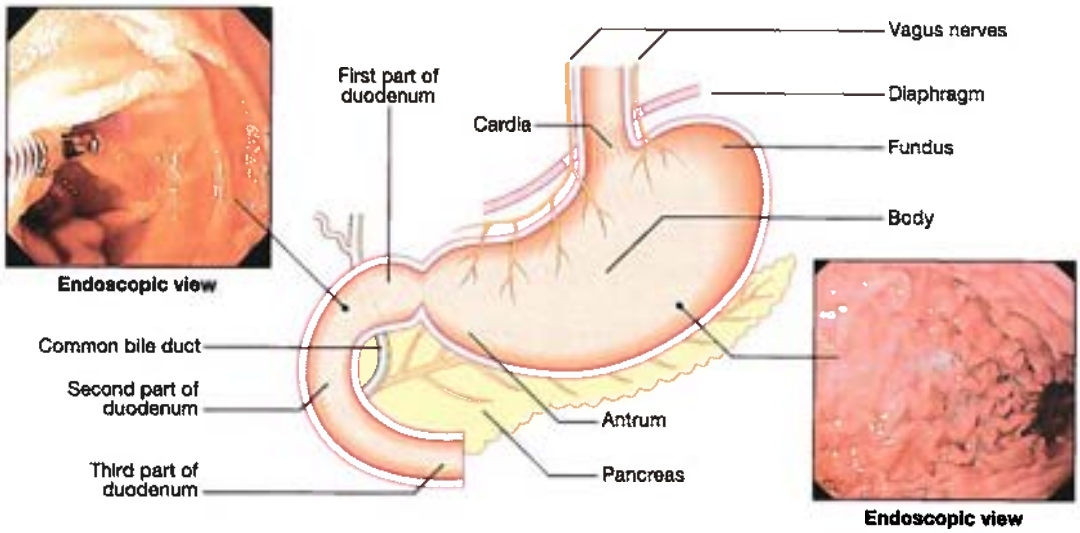
- The biggest surgical challenge is that of anastomotic leak, with an intrathoracic anastomosis resulting in mediastinitis
- In addition to surgical resection many patients will be treated with adjuvant chemotherapy
- Nifedipine helps relieve painful esophageal spasm and tenesmus associated with gastrointestinal tumours and Could be used to relieve his odynophagia.



Barium swallow - 5cm irregular narrowing of the mid-thoracic esophagus with proximal shouldering.

# Stomach and Duodenum

## Gastrointestinal disorders




Normal gastric and duodenal anatomy.

### Dyspepsia

**In 2019 NICE published guidelines for the management of dyspepsia** in primary care. These take into account the age of the patient (whether younger or older than 55 years) and the presence or absence of **'alarm signs'**:
Monomer **ALARMS3**

- Iron deficiency **a**naemia.
- Progressive unintentional weight **l**oss.
- Dysphagi**a.**
- Pe**r**sistent vomiting
- Chronic gastrointestinal bleeding(**m**elena).
- Progressive difficulty **s**wallowing.
- Epigastric ma**ss** (**SWELLING**).
- Suspicious barium meal.

### Deciding whether urgent referral for endoscopy is needed:

Urgent referral (within 2 weeks) is indicated for patients with any alarm signs irrespective of age.

Routine endoscopic investigation of patients of any age, presenting with dyspepsia and without alarm signs is not necessary, however Patients aged 55 years and over should be referred urgently for endoscopy if **dyspepsia** symptoms are:

- Recent in onset rather than recurrent and
- Unexplained (e.g. New symptoms which cannot be explained by precipitants such as NSAIDs) and
- Persistent: continuing beyond a period that would normally be associated with self-limiting problems (e.g. Up to four to six weeks, depending on the severity of signs and symptoms)

## Criteria for referral for urgent endoscopy include:

- Dysphagia (at any age).
- Dyspepsia at any age combined with any one of weight loss, anaemia or vomiting.
- Dyspepsia in a patient aged 55 or above with onset of dyspepsia within one year and persistent symptoms.
- Dyspepsia with one of Barrett's oesophagus, family history of upper gastrointestinal (GI) carcinoma, pernicious anaemia or upper GI surgery more than 20 years ago.
- Jaundice.
- Abdominal mass.

### Managing patients who do not meet referral criteria ('undiagnosed dyspepsia')

**This can be summarised at a step-wise approach:**

- Review medications for possible causes of dyspepsia
- Lifestyle advice
- **Trial of full-dose PPI for one month***
- **Test and treat'** using carbon-13 urea breath test

*it is **unclear** from studies whether a trial of a PPI or a 'test and treat' should be used first.

**NICE** guidelines state in **middle** age group with **dyspepsia**, in the **absence** of **alarm** symptoms, should be **treated with lifestyle advice and PPI** if needed. If after **one month** symptoms are not controlled then **testing for H-pylori** (UBT) could be carried out. There is a need to be a **2 weeks wash-out period off** the PPI for breath test to be reliable.

So, young person with dyspepsia with no alarm signs >>> **prescribe a PPI** and **review symptoms in one month**.

Offer H pylori eradication therapy to people who have tested positive for H pylori and who have peptic ulcer disease.

## Functional Dyspepsia

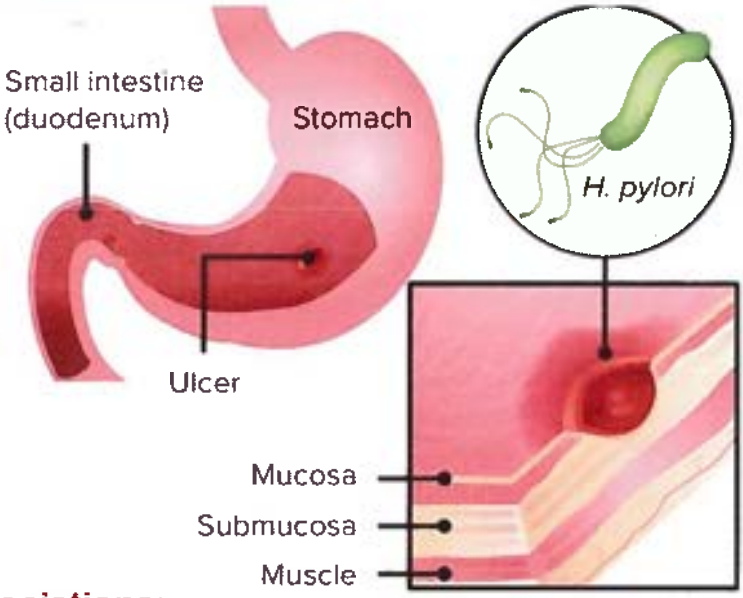
- functional dyspepsia refers to dyspepsia **for which no organic etiology has been determined by endoscopy or other testing**.
- This is the most common cause of chronic dyspepsia, accounting for the majority of patients.
- Symptoms may arise from a complex interaction of increased visceral afferent sensitivity, gastric delayed emptying or impaired accommodation to food or psychosocial stressors or may develop de novo following an enteric infection. Although benign, these symptoms may be chronic and difficult to treat.
- **Manage** endoscopically determined functional dyspepsia using initial treatment for H pylori if present, followed by symptomatic management and periodic monitoring.
- **Offer** eradication therapy to people testing positive for H pylori.
- **Do** not routinely offer re-testing after eradication, although the information it provides may be valued by individual people.
- **If** H pylori has been excluded and symptoms persist, offer either a low-dose PPI or an H2RA for 4 weeks.
- **If** symptoms continue or recur after initial treatment, offer a PPI or H2RA to be taken at the lowest dose possible to control symptoms.
- **Avoid long-term, frequent dose, continuous antacid therapy (it only relieves symptoms in the short term rather than preventing them).**

## Helicobacter pylori (H-Pylori)

Helicobacter pylori is a Gram-negative bacteria associated with a variety of gastrointestinal problems, principally **peptic ulcer disease.**

### Pathophysiology

- Helicobacter pylori has 2 main mechanisms to survive in the acidic gastric environment:
  - chemotaxis away from low pH areas, using its flagella to burrow into the mucous lining to reach the epithelial cells underneath
  - secretes urease → urea converted to $NH_3$ → alkalinization of acidic environment → increased bacterial survival
- pathogenesis mechanism:
  - Helicobacter pylori releases bacterial cytotoxins (e.g. CagA toxin) → disruption of gastric mucosa




## Associations:

- **Peptic ulcer disease (PUD):**
  - **95%** of **duodenal** ulcers (DU),
  - **75%** of gastric ulcers (GU)).
- **Gastric cancer.**
- B cell lymphoma of **MALT** tissue (ttt by eradication of H pylori results causes regression in 80% of patients).
- **Atrophic gastritis.**

**N.B:** The role of H pylori in Gastro-oesophageal reflux disease (GORD) is **unclear** - there is currently **no role** in GORD for the eradication of H pylori.

## Helicobacter pylori: tests

### Urea breath test (UBT):

- Patients consume a drink containing carbon isotope 13 (13C) enriched urea
- Urea is broken down by *H. pylori* urease
- After 30 mins patient exhale into a glass tube
- Mass spectrometry analysis calculates the amount of 13C CO2
- Should not be performed within **4 weeks of treatment with an antibacterial or within 2 weeks of an antisecretory drug (e.g. a PPI).**
- **Sensitivity 95-98%, specificity 97-98%**
- Re-testing for Helicobacter pylori is indicated only in the setting of PUD to confirm **eradication** where an initial test is positive.

**Urea breath test –**
No antibiotics in past 4 weeks, no antisecretory drugs (e.g., PPI) in past 2 weeks.

**Rapid urease test (e.g., CLO test):**

- Biopsy sample is mixed with urea and pH indicator
- Colour change if H pylori urease activity
- Sensitivity 90-95%, specificity 95-98%
- Although rapid urease testing has a sensitivity of 93- 97% the false negative rate increases significantly in the context of:
  - **Recent gastrointestinal haemorrhage**
  - Acid suppression therapy
  - Recent antibiotic treatment.
- **In this case a blood test for Helicobacter pylori infection is required**
- Serological markers would indicate the likelihood of Helicobacter pylori infection and are **unaffected by the factors mentioned above.**

**Serum antibody:**

- **Remains positive** after eradication
- Sensitivity 85%, specificity 80%

**Gastric biopsy**

- Histological evaluation alone, no culture
- Sensitivity 95-99%, specificity 95-99%

**Culture of gastric biopsy**

- Provide information on antibiotic sensitivity
- Sensitivity 70%, **specificity 100%**

**Stool antigen test**

- Sensitivity 90%, specificity 95%.
- Whilst stool antigen testing is appropriate in the setting of initial diagnosis the NICE guidelines on dyspepsia **do not recommend its use to confirm eradication** due to a lack of evidence.
  - it is important to be aware that testing may need to be delayed for **three months after treatment** to confirm eradication.

**Test to confirm eradication :**

- **When to test for complete eradication?**
  - Re-testing for *Helicobacter pylori* is **indicated only in the setting of peptic ulcer** disease to confirm eradication where an initial test is positive,,.
- **Which test?**
  - **Carbon-13 urea breath testing is the only well validated method for confirming the successful eradication of Helicobacter pylori.**

**N.B** The **urea breath test (UBT)** is highly sensitive, specific and non-invasive. There is no indication for an endoscopy. **Stool antigen**, rather than culture, is an alternative.

## Management:

### First line:

**Eradication may be achieved with a 7 day course of:**

- **Not allergic to penicillin**
  - **A proton pump inhibitor + amoxicillin + clarithromycin,**
- **Allergic to penicillin**
  - **A proton pump inhibitor + metronidazole + clarithromycin,**
- **Allergic to penicillin + previous exposure to clarithromycin:**
  - **PPI + bismuth + metronidazole + tetracycline.**

Triple therapy is **for 1 week** as studies now show that 2 weeks of treatment is no more effective than 1 week.

**Two weeks** of therapy is considered when a **MALT lymphoma** has been identified.

### Second-line treatment:

**Offer** people who still have symptoms after first-line eradication treatment a 7-day, twice-daily course of treatment with:

- **PPI + amoxicillin + either clarithromycin or metronidazole (whichever was not used first-line).**

**Offer** people who have had previous exposure to clarithromycin and metronidazole a 7-day course of treatment with:

- **PPI + amoxicillin + quinolone or tetracycline**

**Offer** people who are allergic to penicillin (and who have not had previous exposure to a fluoroquinolone antibiotic) twice-daily course of treatment with:

- **PPI + metronidazole + levofloxacin.**

**Offer** people who are allergic to penicillin and who have had previous exposure to a fluoroquinolone antibiotic:

- **PPI+ bismuth+ metronidazole + tetracycline.**

Seek advice from a gastroenterologist if eradication of H pylori is not successful with second-line treatment.

## Sequential triple therapy for 10 days:

- **First 5 days:** PPI + Amoxicillin
- **Second 5 days:** PPI + Clarithromycin + Tinidazole (Fasigyn®)

**EX**: A man developed **Helicobacter pylori** related duodenal ulcer after **kidney transplantation**. The most reasonable eradication treatment regimen is (**Pantoprazole + Metronidazole + Tetracycline + Bismuth**)

Quadruple therapy containing a PPI, bismuth, metronidazole, and tetracycline, has been shown in meta-analysis of comparative RCTs to achieve a **similar eradication rate** to **clarithromycin-based triple therapy**.

**Clarithromycin** interacts with cyclosporine. Being an **enzyme inhibitor**, this macrolide will result in an (**undesirable**) **increase** the blood level of **cyclosporine**.

H. pylori colonized on the surface of regenerative epithelium (silver stain)

## Gastric MALT lymphoma

### Overview

- associated with H. pylori infection in 95% of cases
- good prognosis
- if low grade then 80% respond to **H. pylori eradication**
- **within the stomach the antrum is most commonly involved**
- account for about 30% of all MALT lymphomas,
- median age of 57 years
- paraproteinemia may be present

### Features

- **paraproteinemia may be present**
- infiltrate of small-size lymphocytes that destroy gastric glands, so-called 'lymphoepithelial lesion which is pathognomonic of lymphoma

- The common cytogenetic abnormalities demonstrated in MALT lymphomas is t (11;18)
- This is clinically important, as t (11;18)-positive cases are Less likely to respond to H pylori- eradication therapy

## Treatment

- **If low grade then 80% respond to H. pylori eradication**
- **Low grade localised gastric helicobacter pylori positive:**
  - **first line**: antibiotics plus a proton-pump inhibitor (PPI)
  - **second line**: radiotherapy
- **Low grade localised gastric helicobacter pylori negative:**
  - **first line**: radiotherapy
- **Low grade advance gastric (Disease not confined to the stomach)**
  - **first line**: chemotherapy
  - **If H pylori – positive >> add eradication therapy**
- **High grade histological transformation:**
  - **First line**: chemotherapy
- **Patients are considered to have failed H pylori eradication when:**
  - there is no regression at repeat endoscopy 2 months after treatment Or
  - when there is lack of complete regression at approximately 18 months after treatment

**MALToma:** B-cell lymphomas characterized by large numbers of immunocompetent cells in the lamina propria. comprising ***large numbers of lymphocytes*** *with* ***irregular nuclear contours*** *and* ***abundant cytoplasm***.
Higher-grade lymphomas show clusters or sheets of blast-like cells.
Up to **75%** of **small low-grade lymphomas** may regress **completely** after antibiotic therapy for **H-pylori eradication**.
Where treatment fails, surgical therapy or combinations with radio- and chemotherapy may be considered.
In addition, **Imatinib mesilate (Glivec)** has recently shown a good deal of success in achieving remission in this condition.

# Peptic ulcer

## Basic

Bleeding from Posterior duodenal ulcers are due to erosion of the gastroduodenal artery

- The right and left gastroepiploic arteries
  - (gastro-omental arteries) supply the greater curvature of the stomach.
- **The right gastric artery** arises from the hepatic artery, supplies the pylorus and travels along the lesser curvature of the stomach, supplying it, and anastomosing with the left gastric artery.
- **The pancreaticoduodenal artery** (a branch of the Gastroduodenal artery) supplies mainly the upper and lower duodenum and the head of the pancreas
- **The right hepatic artery** supplies the right lobe of the liver and part of the caudate lobe

## Sources of bleeding in peptic ulcers

- Greater curvature of the stomach: Left gastroepiploic artery
- Lesser curvature of the stomach: right gastric artery
- **Posterior duodenal ulcers: gastroduodenal artery**
- **pancreaticoduodenal artery (a branch of the gastroduodenal artery) supplies mainly the upper and lower duodenum.**

## Sites of peptic ulcers

- **80% are duodenal.**
- **The most common site >> near the pylorus**, on the duodenal side
- **The less frequent site >> lesser curvature** of stomach or at the point at which the esophagus enters the stomach.

## Risk factors for peptic ulceration

- Helicobacter pylori (H. pylori) infection
- Non-steroidal anti-inflammatory drug (NSAID) use
- cigarette smoking
- Genetic factors - Lewis blood group antigens facilitate H. pylori attachment to the mucosa

## Interventions for peptic ulcer disease

- Peptic ulcer + H pylori >> H pylori eradication therapy
- Retesting for H pylori 6 to 8 weeks after beginning treatment,
- Repeat endoscopy 6 to 8 weeks after beginning treatment

- In people at high risk (previous ulceration) and for whom NSAID continuation is necessary, consider a **COX-2 selective NSAID instead of a standard NSAID with a PPI**
- **Offer H2RA therapy** if there is an inadequate response to a PPI.

## The effect of Helicobacter eradication of peptic ulcer

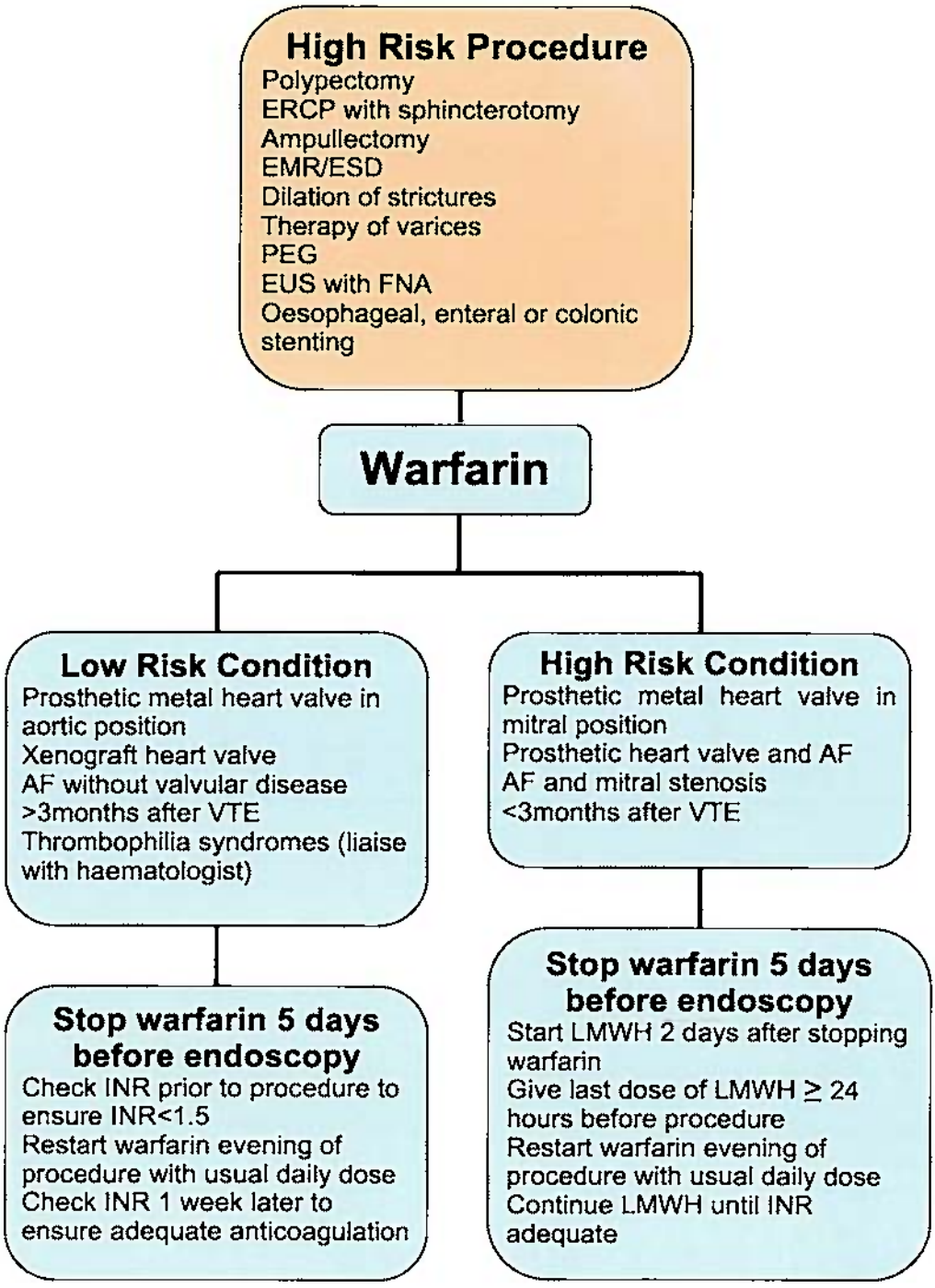
- The effects are dependent upon **whether ulceration is gastric or duodenal** and **whether the patient is taking non-steroidal anti-inflammatory drugs or not.**
- **For Duodenal ulcers** eradication slightly **increases healing** but dramatically **decreases recurrence**
- **For Gastric ulcers** eradication therapy **has no effect on healing but does decrease recurrence**
- In patients taking NSAID eradication therapy has No effect **on healing (gastric or duodenal), but will decrease ulcer recurrence**

## Following endoscopic intervention

- **Immediately post-endoscopy, patients should be commenced on a high dose oral or intravenous proton pump inhibitor**; this reduces the risk of re bleeding.
- Amoxicillin and clarithromycin may be indicated if there is evidence of Helicobacter pylori infection.

## Management of anticoagulation and antiplatelets in endoscopic intervention for bleedinglatelet

- ERCP with sphincterotomy is an endoscopic procedure with a high risk of haemorrhage.
- Clopidogrel is associated with a much higher risk of bleeding than aspirin.
- Ischaemic heart disease without endovascular stents is considered a low risk condition for the temporary discontinuation of clopidogrel.
- Aspirin and clopidogrel are both irreversible inhibitors of platelet function and when they are to be discontinued must be stopped at least 7 days prior to procedure to significantly reduce the risk of associated bleeding.
- Aspirin is not associated with the same degree of bleeding as clopidogrel and may be continued in those already taking it even prior to endoscopic intervention with a high risk of bleeding.
- In those not already prescribed aspirin it should be considered as a bridging agent if clopidogrel must be discontinued.
- Patients with coronary stents in place are at high risk of thrombosis if clopidogrel is discontinued. Their management should be in conjunction with a cardiologist.


High Risk Procedure
Polypectomy
ERCP with sphincterotomy
Ampullectomy
EMR/ESD
Dilation of strictures
Therapy of varices
PEG
EUS with FNA
Oesophageal, enteral or colonic stenting
Warfarin
Low Risk Condition
Prosthetic metal heart valve in aortic position
Xenograft heart valve
AF without valvular disease
>3months after VTE
Thrombophilia syndromes (liaise with haematologist)
High Risk Condition
Prosthetic metal heart valve in mitral position
Prosthetic heart valve and AF
AF and mitral stenosis
<3months after VTE
Stop warfarin 5 days before endoscopy
Check INR prior to procedure to ensure INR<1.5
Restart warfarin evening of procedure with usual daily dose
Check INR 1 week later to ensure adequate anticoagulation
Stop warfarin 5 days before endoscopy
Start LMWH 2 days after stopping warfarin
Give last dose of LMWH ≥ 24 hours before procedure
Restart warfarin evening of procedure with usual daily dose
Continue LMWH until INR adequate

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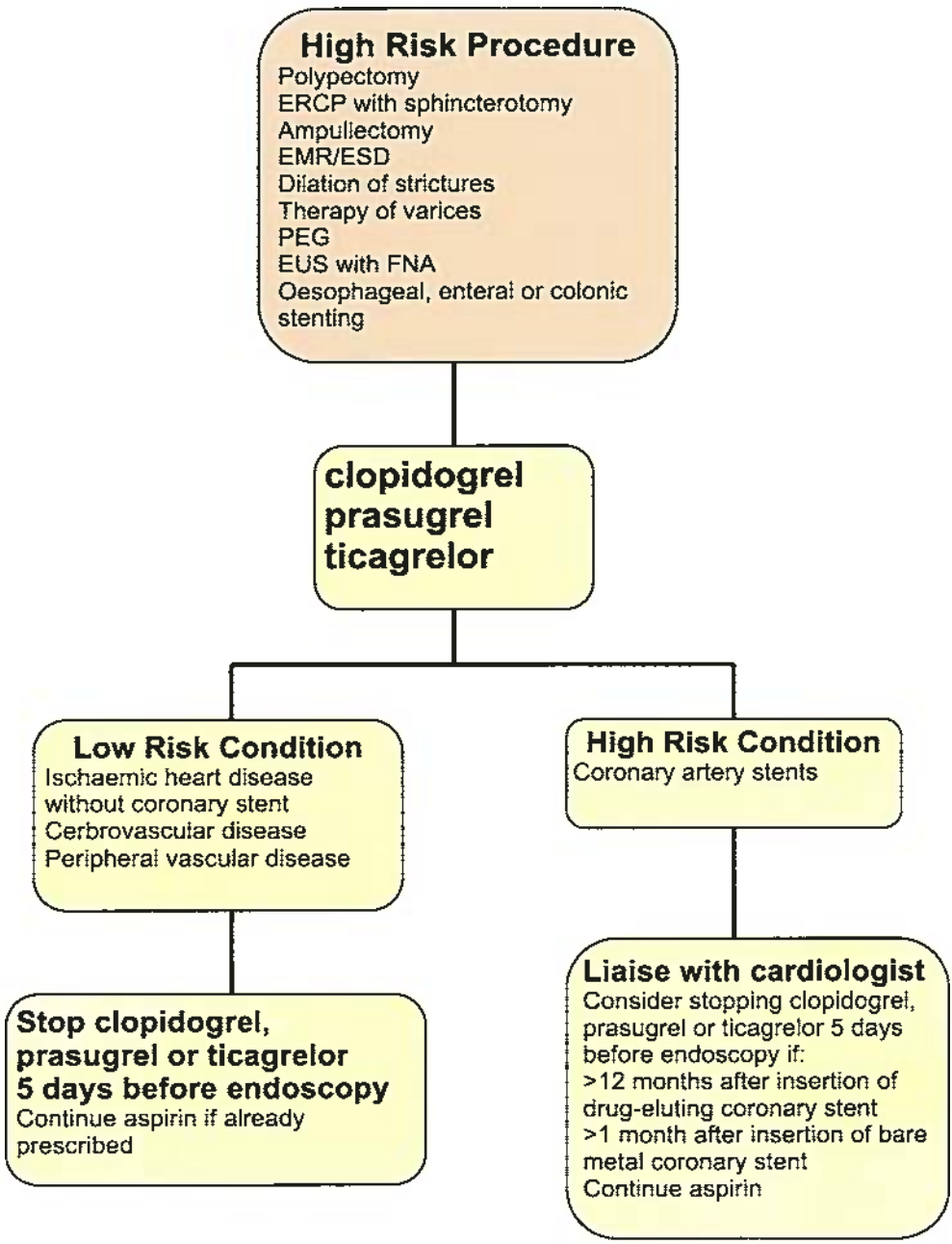


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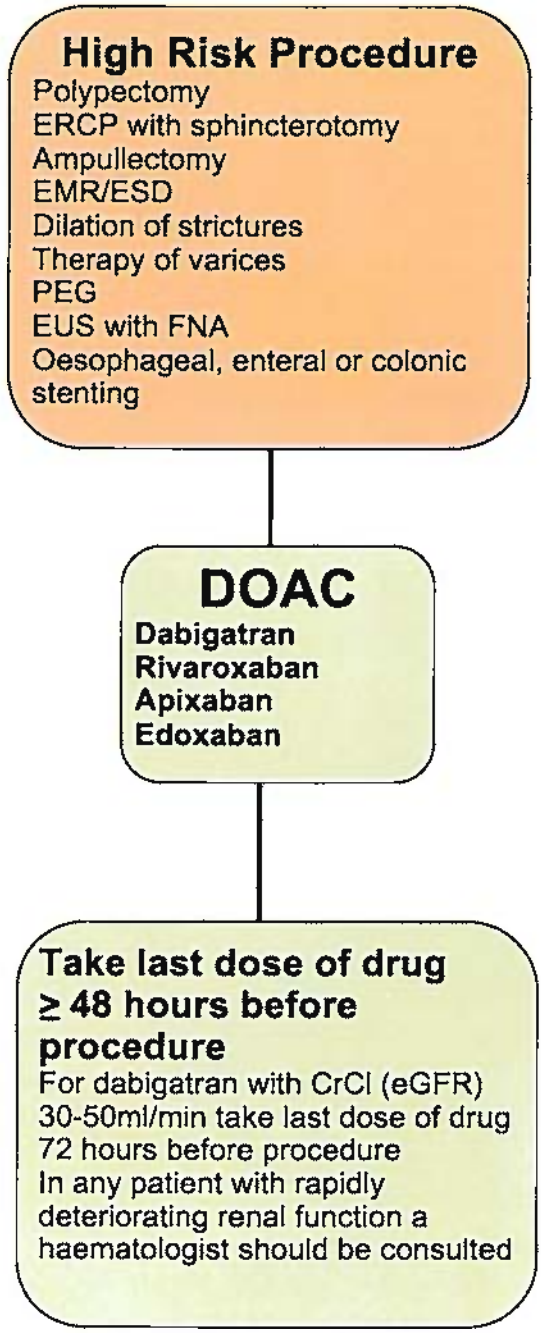


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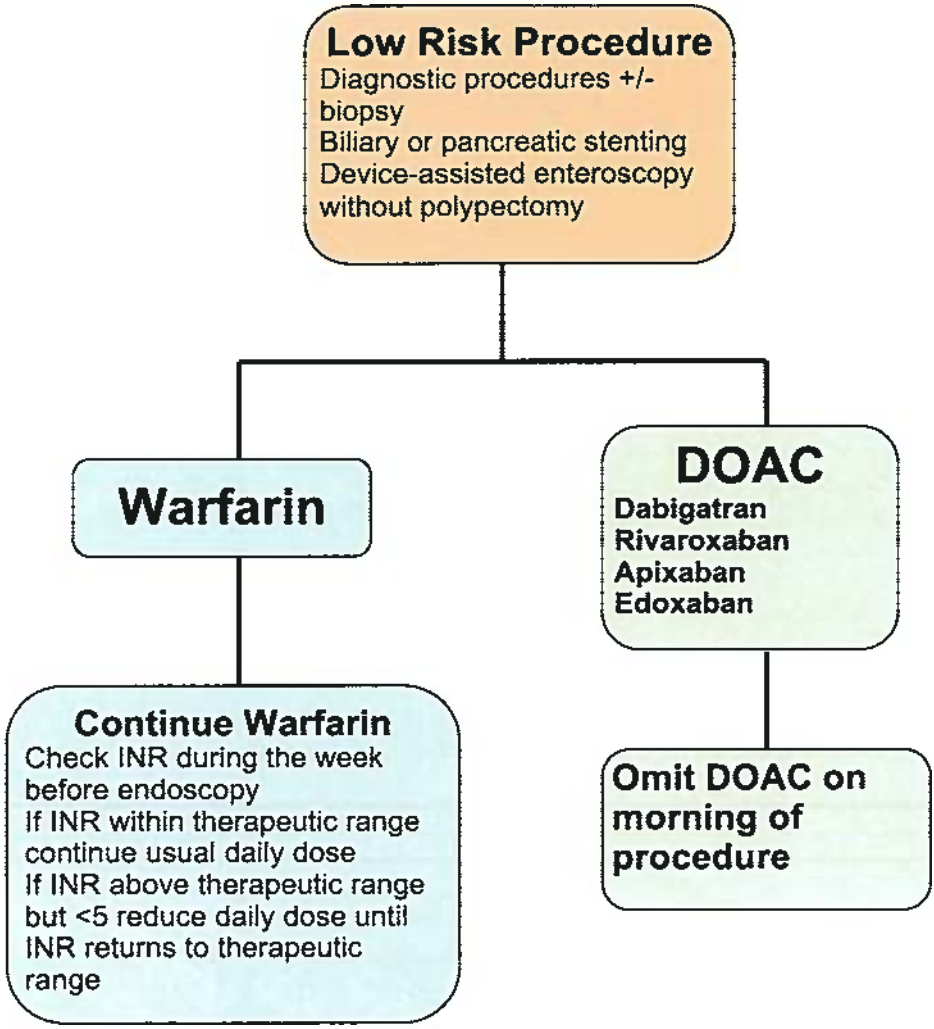
Low Risk Procedure
Diagnostic procedures +/- biopsy
Biliary or pancreatic stenting
Device-assisted enteroscopy without polypectomy
Warfarin
DOAC
Dabigatran
Rivaroxaban
Apixaban
Edoxaban
Continue Warfarin
Check INR during the week before endoscopy
If INR within therapeutic range continue usual daily dose
If INR above therapeutic range but <5 reduce daily dose until INR returns to therapeutic range
Omit DOAC on morning of procedure

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# Zollinger-Ellison syndrome (ZES)

Zollinger-Ellison syndrome is a rare condition characterised by excessive levels of gastrin, usually from a **gastrin** secreting tumour usually of the duodenum or pancreas.
Gastrin is mainly produced in two forms by the **G cells** of the **gastric antrum**. It stimulates the parietal cells to produce HCL and its production is **stimulated** by neural reflex pathways and also by the **direct effect of digested gastric luminal peptides** on the G cells themselves.
Gastrin may have some effect in stimulating exocrine pancreatic secretions.
ZES is under-diagnosed and it is **malignant** in approximately **60%** of cases.
5 years survival rate of 80% for a single tumour.

## Epidemiology

- Sex: ♂ > ♀ (2:1)
- Age of onset: 30–50 years

## Causes

- Most gastrinomas occur sporadically.
- **Around 30% occur as part of MEN type I syndrome.**

## Features:

- **Multiple gastroduodenal ulcers.**
- **Diarrhoea**: may be the only presenting symptom.
- **Malabsorption**: Vit B12 deficiency >> Macrocytic anaemia.

Zollinger-Ellison syndrome (ZES) >> Epigastric pain and diarrhoea

## Tumour location:

- **Duodenum (70% of cases)**
  - Most ulcers are located in the first part of the duodenum.
- **Pancreas (25% of cases)**: typically, the head
- **Ectopic locations (5–15% of cases)**

## Diagnosis:

- **Best initial test: Esophagogastroduodenoscopy**
  - Important to rule out H. pylori infection and malignant ulcers
  - Typically reveals multiple ulcers and thick gastric folds
  - The presence of multiple, large (> 2 cm) ulcers in atypical locations (e.g., the jejunum) should raise suspicion of Gastrinoma
- **Fasting gastrin levels**
- **The single best screen test**
  - Fasting gastrin test > 1000 with low PH < 2 **is diagnostic**
  - If level < 1000 and the diagnosis is suspected, then >> **secretin stimulation testing or calcium stimulation testing**

- Patient should stop PPI for at least 1 week before the test to avoid false positive results,
- It should be done for 3 separate days as the secretion of gastrin is pulsatile
- Three samples in the normal range make a gastrinoma unlikely
- **Secretin stimulation test**
  - **Rise > 200 after 15 minutes of dosing is considered positive**
- **Calcium stimulation test**
  - **Rise > 395 is considered positive**
- **Radioisotope scan**
- **Hot spots of tumour expressing somatostatin receptors**

CT abdomen has a sensitivity of only 50% for primary tumours in ZES. Normal levels of fasting gastrin in untreated ZES are extremely rare.

Other causes of **elevated serum gastrin** is **atrophic gastritis** and **PPI** ttt.

## Treatment:

- Reduce acid production
  - PPIs (e.g., omeprazole), H2 antagonists (e.g., ranitidine)
  - Octreotide (a somatostatin analog) may be used in refractory cases
- Non-metastatic disease
  - surgical resection of the gastrinoma
- Metastatic disease
  - Chemotherapy

## MEN-I:

- Parathyroid (95%): hyperparathyroidism due to parathyroid hyperplasia
- Pituitary (70%): prolactinoma some times GH secretion
- Pancreas (50%): e.g., Insulinoma, gastrinoma (ZES).

Serum **fasting gastrin** levels **above 1,000** (Normal < 200 pg/ ml) with **low gastric pH < 2** are strongly indicative of a **gastrinoma** >>> the patient should be subject to **Secretin stimulation test.**

Secretin is the first choice, and a rise of greater than 200 15 minutes after dosing is a pointer towards a gastrinoma as the underlying diagnosis. **It would be sensible to perform the secretin first, prior to attempting pancreatic imaging.**

He should not be committed to high dose PPI therapy until gastrinoma has been ruled out.

## Somatostatin again

| Source | Action | Regulation | Notes |
|---|---|---|---|
| ▪ D cells (pyloric antrum, and duodenum Mucosa)<br>▪ delta cells (pancreas)<br>▪ ventromedial<br>▪ nucleus of the hypothalamus. | ▪ ↓gastric H+ and pepsinogen secretion<br>▪ ↓pancreatic and small intestine fluid secretion<br>▪ ↓gallbladder contraction<br>▪ ↓insulin and glucagon release<br>▪ ↓GH release | ▪ ↑by H+<br>▪ ↓by vagal stimulation | ▪ Inhibitory hormone<br>▪ Antigrowth hormone effects (digestion and absorption of substances needed for growth)<br>▪ Produce vasoconstriction of the splanchnic system<br>▪ Somatostatin is treatment for VIPoma and carcinoid tumors |

- **Inhibit TSH secretion**
- Mechanism of action
  - Somatostatin receptor is linked to adenylyl cyclase by Gi protein, which inhibits CAMP production and reduces secretion of hormones.

## Somatostatinoma

- Annual incidence →1 in 40 million.
- **Associations:**
  - Impaired glucose tolerance (IGT) or diabetes mellitus (95%)
  - Anaemia (14%)
  - Multiple endocrine neoplasia type 1 (7%)
  - Gallstones (68%)
  - Diarrhoea
  - Weight loss (25%)

### Diagnosis:

- The tumours are often multisecretory →↑↑ **Somatostatin, adrenocorticotropic hormone (ACTH) and calcitonin**
- Contrast spiral computed tomography scanning is effective for detecting the primary tumour in only 50% of cases
- Radiolabeled octreotide or endoscopic ultrasound scanning are often be required.

### Treatment

- surgery is rarely possible due to presence of metastases
- hepatic embolisation can be helpful for symptom control

# Gastroparesis

## Definition

- Delayed gastric emptying in the absence of a mechanical obstruction

## Causes

- Mostly idiopathic but also associated with diabetes mellitus and upper GI surgery.
- Occurs in 10-20% of diabetics after 10 years.

## Mechanism

- The major stimulant for gastric motility is "stretch."
- In patients with longstanding diabetes, there is impaired ability to perceive stretch in the GI tract and impaired motility.

## Symptoms

- erratic blood glucose control
- chronic nausea, vomiting, epigastric pain, bloating
- early satiety, abdominal fullness, constipation.

## Diagnosis

- Gastric-emptying scan
  - Gastric emptying scintigraphy demonstrating >10% retention of the radionuclide meal at the end of 4 hours is diagnostic.

## Management

### Metoclopramide: the first drug of choice

- **Action:** both a dopamine receptor antagonist and a serotonin receptor agonist.
- **Indication:** It is better for short-term treatment. Its use in the long-term treatment of gastroparesis is no longer recommended
- **Side effects:** extrapyramidal

### Domperidone

- **Action:** dopamine antagonist with an affinity for the D2 receptor in the brain and peripheral gastrointestinal system.
- **Indications:** only used for nausea and vomiting and is no longer recommended for the treatment of conditions such as heartburn, bloating, or stomach discomfort.
- **Side effects:** associated with a small increased risk of life-threatening cardiac effects.
- **Advantages:** It does not cross the blood-brain barrier, sO does not cause the neurological adverse effects associated with metoclopramide.

- **Contraindications**
  - Contraindicated in patients with hepatic or cardiac disease.
  - Should not be administered with other drugs that prolong the QT interval or inhibit CYP3A4

**Erythromycin**

- **Action:** ↑release of "motilin, a pro-motility GI hormone.
- used in the acute care setting if the patient is admitted to hospital.

Dietary modification (small, frequent meals that are low in fat and contain only soluble fiber), glycemic control and hydration

Type 2 diabetes with erratic blood glucose control or unexplained gastric bloating or vomitingThink about a diagnosis of gastroparesis.

## Gastric cancer

### Epidemiology:

- The incidence of distal stomach tumours is actually decreasing while the **incidence of tumours in the proximal stomach (the cardia) is increasing.**
- Peak age = 70-80 years.
- More common in **Japan**, China, Finland and Colombia than the West.
- More common in males, 2:1

### Features

- often presents **late,** with **weight loss,** early satiety and postprandial vomiting
- in some cases, **Acanthosis nigricans**
- **leser-trelat sign**
  - Multiple seborrheic keratosis, often with an inflammatory base
  - Associated with **gastrointestinal adenocarcinomas** as part of a paraneoplastic syndrome.
- **Sister Mary Joseph nodule**
  - Is a feature of gastric carcinoma and involves **metastasis to the periumbilical region.**

**Metastasis**

- **The liver is the most common site of metastasis**
- When first diagnosed with gastric cancer, 70% of patients already show metastatic spread to the lymph nodes
- The lymph node most commonly involved >> **left supraclavicular node (Virchow node)**

### Histology

- **Signet ring cells** may be seen in gastric cancer.
  - They contain a large vacuole of mucin which displaces the nucleus to one side.
  - **Higher numbers of signet ring cells are associated with a worse prognosis**

## Associations:

- Chronic **H. pylori** infection
- **Blood group A: gAstric cAncer**
- Gastric adenomatous **polyps**
- **Pernicious anaemia**
- **Smoking**
- **Alcohol**
- Diet: salty, spicy, **nitrates (nitrosamines)** and **smoked foods.**
- Occupational exposure to **heavy metals**, **rubbers**, **asbestos.**
- May be negatively associated with duodenal ulcer

**NSAID** use is associated with **decreased** risk of certain gastric tumours

### Types of gastric adenocarcinoma

#### Diffuse gastric adenocarcinoma

- Characterized by thickening and rigidity of the gastric wall.
- more common in women and individuals less than 50 years old
- These tumours infiltrate the **submucosa**, so that mucosal sampling may not show neoplastic cells.
  - **(Scirrhous infiltration of the submucosa)**
- associated with signet ring cells and linitis plastic
- **Linitis plastica** is a particularly aggressive form of diffuse adenocarcinoma.
  - It is also known as **"leather bottle stomach"**
  - (Because the stomach is diffusely thickened, with a small lumen that cannot expand, leading to the symptom of early satiety)

#### Intestinal type of gastric adenocarcinoma

- The most common type of gastric adenocarcinoma.
- presents as a large, irregular ulcer with heaped up margins,
- Typically, at the lesser curvature of the antrum.

## Investigation

- Diagnosis: endoscopy with biopsy
- Staging: CT or endoscopic ultrasound - **endoscopic ultrasound (EUS) has recently been shown to be superior to conventional CT** as it is able to assess depth of infiltration and lymphatic dissemination of tumour.
- Screening for gastric carcinoma in Japan detects up to 40% of gastric carcinomas at an early stage and in skilled hands **5 year survival** can be upwards of **90%**.
- Laparoscopy to identify occult peritoneal disease
- PET CT

## Management

### Gastrotomy

- proximally sited disease greater than 5-10cm from the OG junction may be treated by subtotal gastrostomy
- Total gastrostomy if tumor is <5cm from OG junction
- For types 2 junctional tumours (extending into esophagus ) esophaggoggastrectomy is usual
- Endoscopic sub muscol resection may play a role in early gastric cancer confined to the mucosa and perhaps the sub mucosa
- Lymphadenectomy should be performed
- Most patients will receive chemotherapy either pre or post operatively

### Iron deficiency is a possible complication of gastrectomy

- **(The body of the stomach** is the primary location for **parietal cells)**
  - Parietal cells produce gastric acid and intrinsic factor
  - Intrinsic factor is necessary for the absorption of vitamin B12
  - Gastric acid > aid the absorption of iron low pH environment is necessary for the reduction of Fe3+ (ferric iron) to Fe2+ (ferrous iron) the absorbable form of iron

## Prognosis

- **Early diagnosis** of gastric carcinoma results in a five-year survival rate of 90%
- At diagnosis, 60% of cancers have already reached an advanced stage that does not allow for curative treatment

# Gastrointestinal stromal tumour (GIST)

- **common type of sarcoma; it develops in the gastrointestinal tract**
- occur most often in adults over the age of 50 years
- Location of GISTs:
  - **Most commonly involve the stomach (60%)**
  - Jejunum and ileum (30%),
  - duodenum (4%–5%)

## Features

- Mostly asymptomatic.
- Tumour induce GI bleed and anaemia
- Abdominal discomfort, early satiety, palpable abdominal mass
- Bowel obstruction or perforation
- Dysphagia

## Management

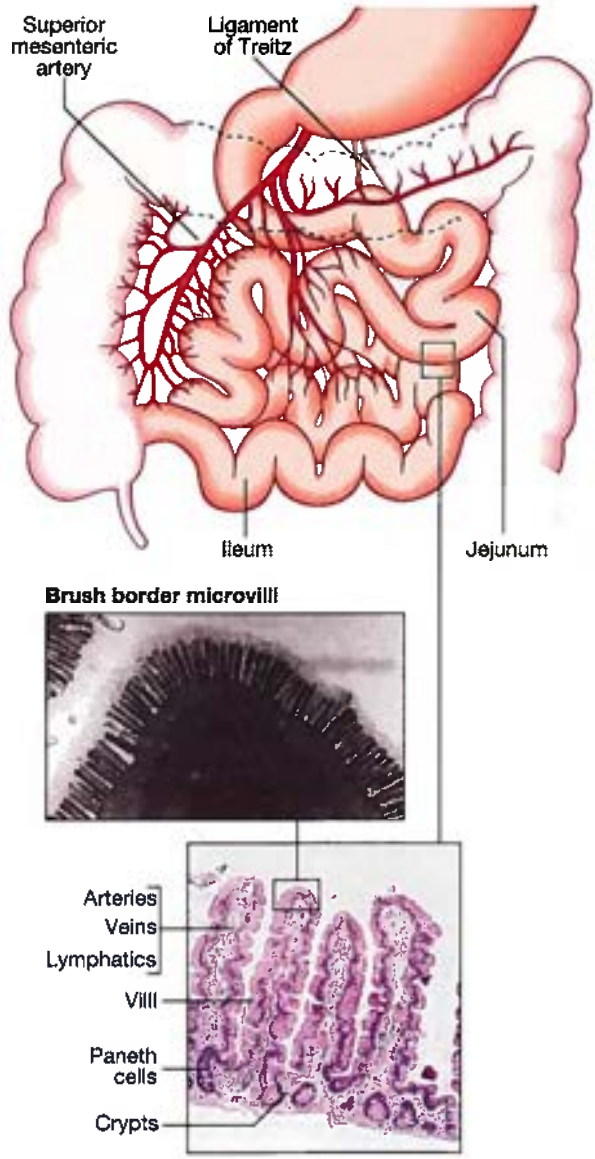
- all GISTs ≥ 2 cm >> surgery
  - Surgery is usually the first treatment method used for GIST.
  - If the tumour is too large to be removed at the time of diagnosis, it may be treated initially with imatinib.
  - If sufficient shrinkage has occurred after 6-12 months, it may be operated.
- GISTs < 2 cm: watchful waiting and surveillance
- for patients with KIT-positive unresectable and/or

Metastatic GIST >> **Medical Management:**

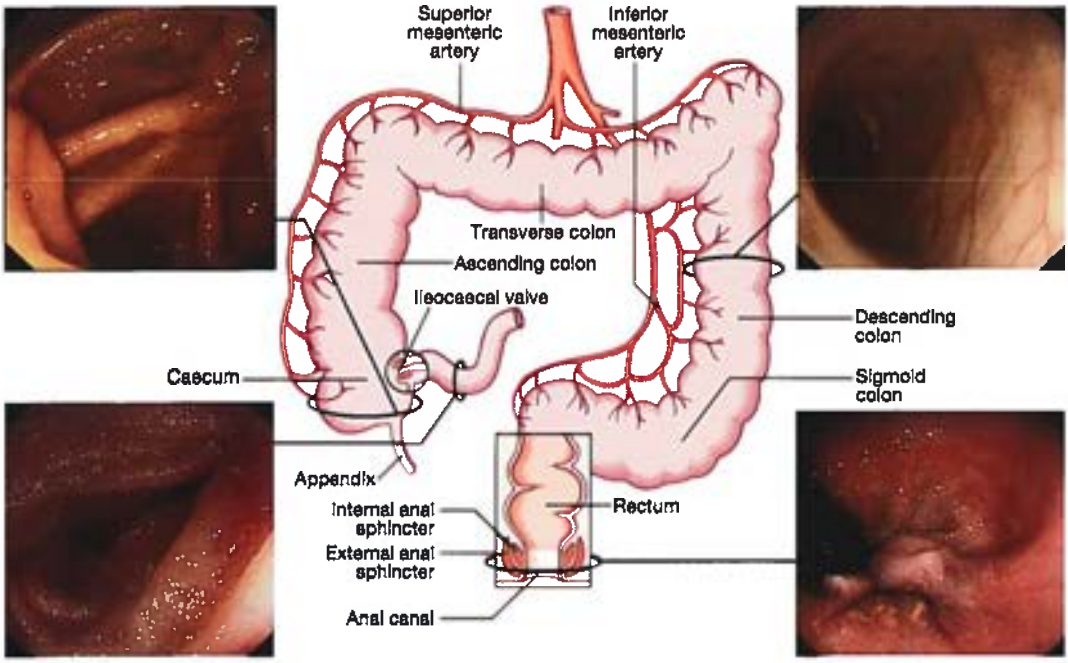
# Small and Large Intestine

## intestinal disorder

### Basic anatomy and histology of the small and large intestine




Small intestine: anatomy. Epithelial cells are formed in crypts and differentiate as they migrate to the tip of the villi to form enterocytes (absorptive cells) and goblet cells.




The normal colon, rectum and anal canal.

## VIPoma

VIPoma is a vasoactive intestinal polypeptide (VIP) secreting tumour occurring mainly in the **pancreas**.
It is a gut neuroendocrine tumour
It is rarely a ganglioneuroblastoma (sympathetic chain or adrenal cortex).

### The normal functions of VIP are:

- **Peripheral vasodilation**
- Increased intestinal secretion of water and electrolytes
- Inhibition of gastric acid secretion, and
- Potentiates acetylcholine action on salivary glands.

**VIPomas are** endocrine tumours that secrete excessive amounts of VIP 32 which cause a distinct syndrome characterised by:

- **90% arise from pancreas**
- **Large-volume watery diarrhoea** (usually **more than 700 mL/day**)
- **Dehydration**.
- weight loss

- **Acidosis** (due to loss of alkaline secretions)
- **hypokalaemia, hypochlorhydia**
- **Hypergylcaemia**
- **Serum Chromogranin A** is **elevated** in the majority of neuroendocrine tumours with the exception of Insulinoma.
- abdominal colic
- cutaneous flushing
- raised plasma VIP

This syndrome is also called **Verner-Morrison syndrome**, **pancreatic cholera**, or **WDHA syndrome** for: **W**atery **D**iarrhoea, **H**ypokalaemia, and **A**chlorhydria, which some patients develop.

It can occur in children and when it does is usually caused by a ganglioneuroma or ganglioneuroblastoma.

## Treatment:

- **Medical** management of choice is with **somatostatin analogues**, often small doses lead to a cessation of symptoms.
- **Codeine** prolongs small bowel transit time and increases stool water absorption; it may be an adjunct in patients who do not adequately respond to somatostatin.
- Non-metastatic tumours can be surgically resected.

**A stool volume of <700 mL/d excludes the diagnosis of VIPoma.**

**Achlorhydria** is classically associated with VIPoma together with **profuse diarrhoea**, a **hypokalaemic acidosis** and **hyperglycaemia**.

Although raised pancreatic polypeptide is seen with a VIPoma it is unusual and is more commonly associated with its own syndrome.

**NB**: Migratory erythema is associated with a Glucagonoma.

**NB**: Pellagra is associated with the carcinoid syndrome.

## Dumping syndrome

Occur in up to 50% of patients who have undergone gastric bypass when high levels of simple carbohydrates are ingested.

### Early dumping syndrome

- rapid onset, usually within **15 minutes of eating**
- **Results from rapid emptying of food into the small bowel**
- Due to the hyper osmolality of the food, there are rapid fluid shifts from the plasma into the bowel leading to hypotension and a sympathetic nervous system response.
- The presenting symptoms are often colicky abdominal pain, diarrhoea, nausea, and tachycardia.

### Treatment

- **Usually self-limiting and resolves within 7 to 12 weeks**
- Patients should avoid foods high in simple sugar and replace them with high fibre, complex carbohydrates and protein-rich foods.
- Small, frequent meals
- leaving a 30-minute gap between solids and liquids

### Late dumping syndrome

- **Occurs as a result of the hyperglycaemia and subsequent insulin response leading to hypoglycaemia** which takes place two to three hours after a meal.
- Symptoms include dizziness, fatigue, sweating, and weakness.
- **Management is similar to early dumping syndrome**

## Small bowel bacterial overgrowth syndrome (SBBOS)

SBBOS is a disorder characterised by excessive amounts of bacteria in the small bowel resulting in gastrointestinal symptoms.

**$B_{12}$ deficiency (macrocytic anaemia)** is caused by bacterial overgrowth. It is very unusual in patients without risk factors for the condition.

**Steatorrhea** and **flatulence** are classic presenting features of SBBOS.

### Risk factors for SBBOS:

- **Neonates** with congenital gastrointestinal abnormalities
- **DM**
- **Inflammatory bowel disease (IBD: CD/UC)**
- **Diverticulosis**
- **Scleroderma**

It should be noted that many of the **features overlap** with **IBS**:

- Abdominal pain
- Bloating, flatulence
- **Chronic diarrhoea**

### Diagnosis:

- **hydrogen breath test**
- small bowel aspiration and culture: this is used less often as invasive and results are often difficult to reproduce
- clinicians may sometimes give a course of antibiotics as a diagnostic trial

### Management:

- Correction of underlying disorder.
- Antibiotic therapy:
  a. **Rifaximin**, a non-absorbable form of Rifampicin, is now the treatment of **choice** due to relatively low resistance.
  b. Co-amoxiclav or metronidazole or tetracyclines is also effective in the majority of patients.
- If this is failed, jejunal aspiration is recommended to identify the organism.

**N.B** Tetracyclines are no longer commonly used due to widespread bacterial resistance.

**EX**: Male pt. 70 years old with **left iliac fossa tenderness**, **fever**, **intermittent diarrhoea**, **High TLC**, **Urine**: red cells +, white cells + (due to periureteric inflammation) >>> **Diverticulitis** >>> **CT** to assess severity, degree of local infiltration, possible perforation or abscess formation. Medical ttt by **IV antibiotics** and surgical opinion is crucial.

## Malabsorption

Malabsorption is characterised by diarrhoea, steatorrhea and weight loss. Causes may be broadly divided into intestinal (e.g. villous atrophy), pancreatic (deficiency of pancreatic enzyme production or secretion) and biliary (deficiency of bile-salts needed for emulsification of fats).

### Intestinal causes of malabsorption:

- **Coeliac** disease
- **Crohn's** disease
- **Tropical** sprue
- **Whipple's** disease
- **Giardiasis**
- Brush border **enzyme** deficiencies (e.g. lactase insufficiency)

**Pancreatic causes of malabsorption:**

- **chronic** pancreatitis
- **cystic fibrosis**
- pancreatic **cancer**

**Biliary causes of malabsorption:**

- biliary obstruction
- **primary biliary cirrhosis**

**Other causes:**

- bacterial overgrowth (e.g. **systemic sclerosis**, diverticula, blind loop)
- **short bowel syndrome**
- **lymphoma**

## Jejunal villous atrophy

Whilst coeliac disease is the classic cause of jejunal villous atrophy there are a number of other causes you need to be aware of

**Causes:**

- **Coeliac** disease
- **Tropical** sprue
- **Whipple's** disease
- Gastrointestinal **lymphoma**
- **Hypogammaglobulinaemia**
- Lactose intolerance (Cow's milk intolerance).
- Laxative abuse
- Neomycin therapy
- Infectious enteritis
- Giardiasis.
- Norwalk agent.

# Coeliac disease

The prevalence of coeliac disease is **1% in western societies** and is thus **one of the commonest immune-mediated diseases**. But diagnosis is often missed especially in milder forms, **NICE recommend testing for coeliac disease before labelling any patient with irritable bowel disease.**

**The prevalence of coeliac disease in Europe varies widely and is in the region of between 1:100 and 1:300** and as much as **1:30** in the **west of Ireland.** It is more common in the Celtic population.

The condition is caused by an **immunological reaction** to the **gliadin**, a protein fraction of **gluten** found in **wheat,** which provokes an inflammatory response and results in partial or total **villous atrophy** in the **proximal small bowel** (which resolves with a gluten-free diet).

Repeated exposure leads to **villous atrophy** which in turn causes **malabsorption**.

It is strongly associated with **HLA-DQ2, HLA-DQ8** (**95%** of patients) and HLA-B8 (80%) as well as HLA-DR3 and HLA-DR7. and also, from the specific immune response to the alpha-gliadin component of gluten.

The action of tissue transglutaminase (TTG) on alpha-gliadin generates epitopes to **CD4+ T-lymphocytes,** which provoke an inflammatory response in the intestinal wall.

Coeliac disease results from **small bowel inflammation and atrophy** due to **T cell mediated hypersensitivity reaction** to the alpha-gliadin component of gluten.
Other T-cell mediated autoimmune disorders may be associated with coeliac disease: **Type I DM, dermatitis herpetiformis** and **Hashimoto's thyroiditis**.

NICE issued guidelines on the investigation of coeliac disease. They suggest that the following patients should be screened for coeliac disease:

| Signs and symptoms | Conditions |
|---|---|
| • **Unexplained iron-deficiency anaemia**, or other unspecified anaemia is the **most common** presentation of coeliac disease with positive **FOB in 50%** of cases.<br>• **Chronic diarrhoea/ steatorrhoea (ONLY** in **30% of cases** of coeliac).<br>• Persistent or unexplained gastrointestinal symptoms including nausea and vomiting.<br>• Prolonged fatigue ('tired all the time').<br>• Recurrent abdominal pain, cramping or distension.<br>• Sudden or unexpected weight loss.<br>• Failure to thrive or faltering growth (in children). | • Autoimmune **thyroid** disease (**Hashimoto's**).<br>• **Type 1 DM**.<br>• **Dermatitis herpetiformis**.<br>• **Irritable bowel syndrome.**<br>• First-degree relatives (parents, siblings or children) with coeliac disease. |

Symptoms of Coeliac disease are often **mild** and **non-specific** which is why the diagnosis is **missed** if there is not a high index of suspicion.

It can occur at **any age** and is usually present with **diarrhoea**, **weight loss**, **lethargy**, **anaemia** (Fe, B12, folic), **skin itchy rash** (dermatitis herpetiformis).

If you see a **young** patient with **nutritional deficits** (B12, folate, iron) then you should check antibodies.

In **women aged less than 50 years** who **menstruate regularly**, menstrual blood loss is a common cause of IDA, although **coeliac disease** with minimal symptoms is recommended as initial step screening.

**Young** pt. with **IDDM** and **anaemia** >>? Coeliac disease >> check (**TTG IgA**).

**NB:** Coeliac disease may cause malabsorption of iron and folate causing and anaemia with either micro- or macrocytosis.
Sometimes the **MCV** may be **'normal'** due to a deficiency of **both** causing a **bimodal distribution** of red cell volumes which has an average in the normal range.
If patients have additional reasons to be deficient in either folate or iron (e.g., menorrhagia in women) then that may dominate the clinical picture.

**NB**: **Howell-Jolly bodies** on blood film indicate **hyposplenism** and are consistent with a diagnosis of coeliac disease.
Patients with coeliac disease often have a degree of **functional hyposplenism**. For this reason, all patients with coeliac disease are **offered the pneumococcal vaccine.**

## Diagnosis:

Diagnosis of coeliac disease is made by a combination of **immunology** and **jejunal biopsy**.

**NB**: Villous atrophy and immunology normally reverses on a gluten-free diet.

NICE issued guidelines on the investigation of coeliac disease. If patients are already taking a gluten-free diet they should be asked, if possible, to reintroduce gluten (i.e., the patient should eat some gluten in more than one meal every day) for at least 6 weeks before further testing.

**Immunology**:

- Tissue transglutaminase (TTG) antibodies (IgA) are **first-choice**, it has very high sensitivity and specificity of 100%.

Coeliac disease – (**TTG IgA**) tissue transglutaminase antibodies **first**-line test

- This test may be invalid in the presence of selective IgA deficiency, which is much commoner in patients with coeliac disease (2.6%).
  If pt. tested negative with high index of suspection IGA level must be tested, if low then proceed for **IgG BASED TTG test.**

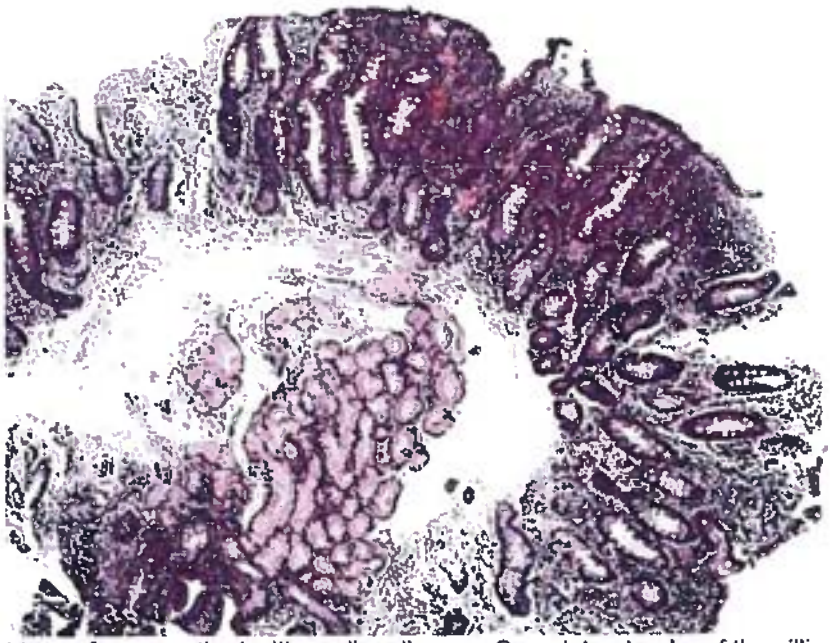
**NB**: Patients normally need to be following a gluten-free diet (GFD) for at least 6 months before the serology becomes negatives.

- Anti-Endomyseal antibody (EMA) (IgA).
- Anti-casein antibodies are also found in some patients.
- Anti-gliadin antibody (IgA or IgG) tests are not recommended by NICE.

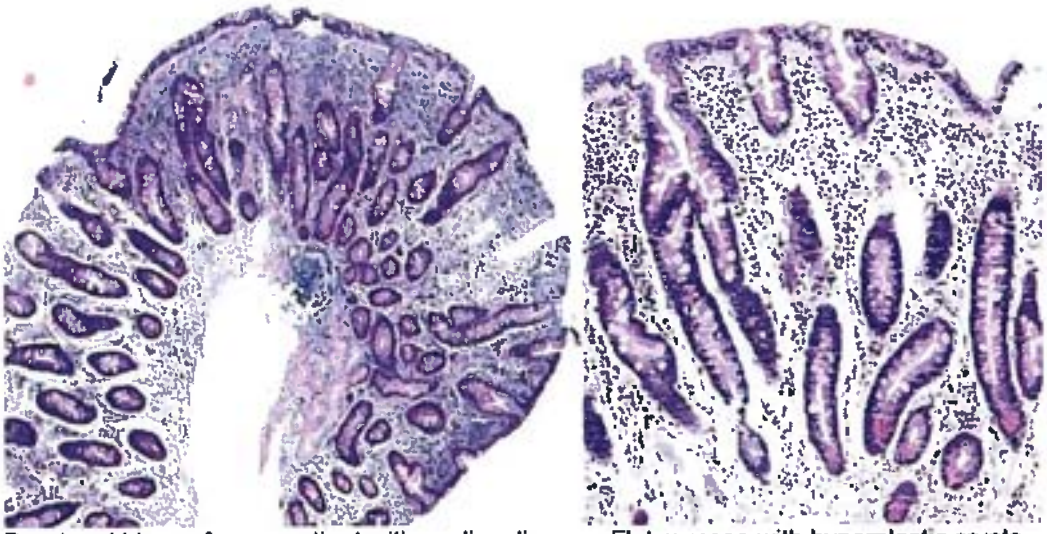
**Jejunal biopsy:** (Appearances may resemble severe **tropical sprue**):

- **Villous** atrophy.
- **Crypt** hyperplasia/hypertrophy.
- Increase in intraepithelial **lymphocytes**
- Lamina propria infiltration with **lymphocytes**

**Rectal gluten challenge has been described but is not widely used**



Duodenal biopsy from a patient with coeliac disease. Complete atrophy of the villi with flat mucosa and marked crypt hyperplasia. Intraepithelial lymphocytosis. Dense mixed inflammatory infiltrate in the lamina propria.



Duodenal biopsy from a patient with coeliac disease. Flat mucosa with hyperplastic crypts and dense cellular infiltrate in the lamina propria. Increased number of intraepithelial lymphocytes and vacuolated superficial epithelial cell vacuolated superficial epithelial cells. Higher magnification image on the right.

## Complications:

- Anaemia: iron, **folate** and vitamin B12 deficiency. (Folate deficiency is more common than vitamin B12 deficiency in coeliac disease).
- **Hypo**-splenism: **Howell-Jolly bodies** on blood film.
- **Osteomalacia** (↓Ca, ↑ ALP) due to **Vit D deficiency** due to its malabsorption with **subsequent hyperparathyroidism**.
- Osteoporosis.
- **Malabsorption**, **low serum albumin** and **weight loss**
- Lactose intolerance.
- **Subfertility,** unfavourable pregnancy outcomes.
- **Oesophageal cancer** (rare).
- **Enteropathy-associated T-cell lymphoma of small intestine**: It is associated with increased risk of developing **small bowel lymphoma**, which thankfully only occurs in a very small portion of coeliac patients, which gives a clinical and radiological picture of **small bowel obstruction.**

Long term risks associated with coeliac disease include **oesophageal carcinoma** and **small bowel lymphoma**, particularly in patients who fail to follow the gluten free regimen.

## Management:

**gluten-free diet.** Gluten-containing cereals include:

**monimenic: WO2BR**

- wheat: bread, pasta, pastry
- barley:
- beer
  - whisky is made using malted barley. Proteins such as gluten are however removed during the distillation process making it safe to drink for patients with coeliac disease
- rye
- oats
  - some patients with coeliac disease appear able to tolerate oats.

**Some notable foods** which are gluten-**free** include

- **Rice**
- **Potatoes**
- Corn **(maize)**

**Immunisation**

- Patients with coeliac disease often have a degree of **functional hyposplenism**

- For this reason, all patients with coeliac disease are **offered the pneumococcal vaccine**
  - Coeliac UK recommends that everyone with coeliac disease is vaccinated against pneumococcal infection and has a booster every 5 years
- Currrent guidelines suggest giving the influenza vaccine on an individual basis.

Folate, iron and calcium supplements may be required.

**EX**: Male patient 44 years old, 10-months history of pain in low back, hips, ankles and feet, tiredness, loss of weight despite eating reasonable meals, pale, anaemia Hb 7, low MCV, positive FOB, low albumin, low calcium, high PTH, prolonged INR >>> **Coeliac disease** with **malabsorption** of iron (IDA), Ca, Vit D (osteomalacia) and Vit K (impaired clotting), associated autoimmune hypothyroidism.

**EX**: Female pt. 16 years old with loose motions for 8 weeks, loss of weight, lethargy, anaemia Hb 9 gm%, itchy rash over both elbows >>> **Coeliac** disease associated with **dermatitis herpetiformis**.

**EX**: Male pt. 60 years old known to have coeliac disease and presented with a clinical and radiological picture of **small bowel obstruction** >>> **small bowel lymphoma** (malignant transformation of coeliac to small bowel lymphoma).

**EX**: Male pt. 40 years old known to have **Coeliac disease**, he has significant **weight loss** and **night fever** >>> **Enteropathy-associated T-cell lymphoma of small intestine**.
Poor compliance to coeliac diet may increase the propensity for malignancy.

**EX**: Female pt. 15 years old has **primary amenorrhoea**, **loss of weight**, low BMI, **occasional diarrhoea**, **anaemia Hb is 10 gm%**, low FSH, low LH, and low Oestradiol but with normal testosterone, normal TSH, **low albumin** >>> **Coeliac disease not** anorexia nervosa.

## Tropical sprue

It occurs in **tropical area**, predominantly **Central America** and **South-Eastern-Asia** (e.g., **Thailand trip**).

It is thought that an initial GI infection results in small bowel stasis, opportunistic colonisation by organisms such as **coliforms**, and then a

degree of **villous atrophy** leading to **malabsorption** and B12, folate deficiency.

**Jejunal biopsy:** villous atrophy, increased crypts and mononuclear cell infiltrates, lipid accumulation below the basement membrane and **coliforms** bacteria may be isolated.

### Treatment:

- **Prolonged course of Tetracycline** for 3-6 months (**avoid pregnancy** while taking the antibiotics).
- Vitamin replacement
- Ampicillin may be used as an alternative in patients who are intolerant of tetracyclines.
- Folate and B12 deficiencies should also be corrected

## Whipple's disease

Whipple's disease is **rare, multi-system** but potentially **fatal** condition and affects most commonly **middle-aged males 40-60 years**.

It can affect **any organ**, but dominated by involvement of **small bowel**, causing **malabsorption >> chronic diarrhoea**.

The causative organism is (**Tropheryma whippelii**), a Gm **positive** bacterium.

It is due to abnormal host immune response to the intracellular organism **Tropheryma whippelii.**

The main triad symptoms include: **weight loss (> 90%), diarrhoea (> 70%), & seronegative arthropathy (> 70%).**

**Non-neurological manifestations** of Whipple's disease are more common and include **chronic diarrhoea**, malabsorption with steatorrhoea and associated abdominal distension and tenderness.

**Neurological manifestations** involve a chronic progressive impairment of higher **mental** function in association with **seizures**, myoclonus **ataxia** and **oculomasticatory myorhythmia** found uniquely in Whipple's.

**Cardiac** complications (in 30%) including: **pericarditis, Endocarditis valvular heart disease** and **conduction defects**.

**Pulmonary** involvements: pleurisy and lung infiltrates.

**Biochemical** abnormalities: **systemic inflammatory response** (high ESR & CRP) and **anaemia** and **Hypoalbuminaemia** due to malabsorption.

**The diagnosis is made by duodenal or jejunal biopsy** and demonstrating the **Tropheryma whippelii bacilli** within the mucosa on **PAS** staining.

Characteristically, there is accumulation of glycoprotein and fat filled periodic acid-Schiff (PAS +ve) **macrophage** within the **lamina propria** with **flattened mucosa (Macrophages with PAS stain +ve granules/sickle-like inclusion bodies**).

**Electron microscopy (E/M):** widened, flattened villi with small **Gram-positive bacilli seen inside the macrophages.**

**PCR DNA for Trophyrema Whippelii in the affected tissue**: it is **very diagnostic** and a best way to detect **remission** after prolonged therapy.

The disease is **fatal** if untreated, but there is usually a good response to antibiotic therapy (penicillin, tetracycline or sulphonamides)

## Treatment

guidelines vary: oral co-trimoxazole for a year is thought to have the lowest relapse rate, sometimes preceded by a course of IV penicillin

**Other option:**

an initial IV penicillin and streptomycin for 2 weeks, followed by one year of tetracycline.

Relapse occurs in 30% of patients and therefore long-term follow-up is essential

EX: Middle-aged pt. attends clinic with his partner who tells you that he has **memory** problems + **chronic intermittent diarrhoea** over few months + limited vertical **eye** movements and exhibits rhythmic simultaneous eye and mouth movements + recurrent fever and arthralgia >> **Whipple's disease** due to intestinal infection with **Tropheryma whippleii**.

Creutzfeldt-Jakob disease (CJD) could also produce this picture, although myoclonus is usually more of a feature and cognitive impairment is more generalised and acute.

Whipple = **Chronic diarrhoea** (weight loss, steatorrhoea), **Neuro**, **Arthralgia**, **Pyrexia**, **Lymphadenopathy**.

## Lactose intolerance

Lactase acts on lactose to generate glucose and galactose.

Lactose intolerance is least common in white northern Europeans and is **more common in Asian, and East Asian races**.

Lactose intolerance may be diagnosed with a **DNA assay of the lactase gene** along with a **hydrogen breath test**.

**Any GI infection (e.g., Rotavirus infection) may reveal lactose intolerance** as gut flora may be altered by large bowel bacterial or viral load, as well as the treatment of infection.

A change from an Eastern to a Western high lactose diet may also reveal lactose intolerance.

Many patients labelled as having IBS may suffer from undiagnosed lactose intolerance and many medications use lactose as a binding and stabilising agent.

**Treatment** of lactose intolerance is with **careful replacement of lactase**.

## Irritable bowel syndrome

**NICE GUIDELINES 2017 AND ROME 4 CRITERIA**

Initial diagnosis of irritable bowel syndrome
Consider diagnosing **IBS** only if the person has abdominal pain or discomfort that is:

- **relieved by defecation, or**
- **associated with altered bowel frequency or stool form and at least 2 of the following:**
- altered stool passage (straining, urgency, incomplete evacuation)
- abdominal bloating (more common in women than men), distension, tension or hardness
- symptoms made worse by eating
- passage of mucus.

Lethargy, nausea, backache and bladder symptoms may be used to support diagnosis.

**Red flag features should be enquired to indicate further workup or challenge the diagnosis:**

- Rectal bleeding/ Rectal mass (not due to fissures or haemorrhoids)
- Anaemia
- Abdominal mass
- Unexplained/unintentional weight loss
- Dehydration
- Steatorrhea
- Family history of bowel or **ovarian cancer**
- Onset after **60** years of age.
- A **change** in bowel habit to **looser** and/or **more frequent** stools persisting for **more than 6 weeks** in a person aged over 60 years.
- Unintentional and unintended weight loss.
- Inflammatory markers for inflammatory bowel disease.
- Fever
- Progressive deterioration

NICE guidelines state that in the presence of a history classical for IBS (and the absence of red flag symptoms such as weight loss) the following are sufficient to exclude other causes of bowel symptoms:

**Suggested primary care investigations are: (3)**

1) CBC
2) ESR/CRP
3) Coeliac disease screen (TTG-IgA) (tissue transglutaminase Ab)

**Confirming a diagnosis of irritable bowel syndrome in people who meet the diagnostic criteria**

## Faecal calprotectin testing

**Fecal calprotectin testing is recommended as an option to support clinicians with the differential diagnosis of IBD or IBS in adults with recent onset lower gastrointestinal symptoms for whom specialist assessment is being considered, if:**

- cancer is not suspected, having considered the risk factors (for example, age) described in the recommendations on lower gastrointestinal tract cancers **in NICE's guidance on suspected cancer recognition and referral**, and
- appropriate quality assurance processes and locally agreed care pathways are in place for the testing.

**N.B** NICE recommends that **thyroid function tests** are **not** necessary prior to making a positive diagnosis of IBS.

## Management:

### Diet

Assess diet and nutrition and give the following general advice:

- Have regular meals and take time to eat.
- Avoid missing meals or leaving long gaps between eating.
- Drink at least 8 cups of fluid per day, especially water or other non-caffeinated drinks such as herbal teas.
- Restrict tea and coffee to 3 cups per day.
- Reduce intake of alcohol and fizzy drinks.
- Consider limiting intake of high-fiber food (for example, whole meal or high-fiber flour and breads, cereals high in bran, and whole grains such as brown rice).
- Reduce intake of 'resistant starch' (starch that resists digestion in the small intestine and reaches the colon intact), often found in processed or re-cooked foods.
- Limit fresh fruit to 3 portions (of 80 g each) per day.
- For diarrhea, avoid sorbitol, an artificial sweetener found in sugar-free sweets (including chewing gum) and drinks, and in some diabetic and slimming products.
- For wind and bloating consider increasing intake of oats (for example, oat-based breakfast cereal or porridge) and linseeds (up to 1 tablespoon per day).

### First-line pharmacological treatment

First-line pharmacological treatment - according to predominant symptom

- pain: antispasmodic agents
  - Pinaverium is used to reduce the pain duration associated with (IBS)
- constipation: laxatives but avoid lactulose
- diarrhoea: loperamide is first-line

**NICE has published an evidence summary on irritable bowel syndrome with constipation in adults: linaclotide.**

**For patients with constipation who are not responding to conventional laxatives linaclotide may be considered, if:**

- optimal or maximum tolerated doses of previous laxatives from different classes have not helped and
- they have had constipation for at least 12 months
- Advise people how to adjust doses of laxative or antimotility agent according to response, shown by stool consistency. The aim is a soft, well-formed stool **(Bristol stool form scale type 4).**

### Second-line pharmacological treatment:

- low-dose tricyclic antidepressants (e.g., amitriptyline 5-10 mg) are used in preference to selective serotonin reuptake inhibitors

### Other management options

- psychological interventions - if symptoms do not respond to pharmacological treatments after 12 months and who develop a continuing symptom profile (refractory IBS), consider referring for cognitive behavioural therapy, hypnotherapy or psychological therapy
- complementary and alternative medicines: 'do not encourage use of acupuncture or reflexology for the treatment of IBS'

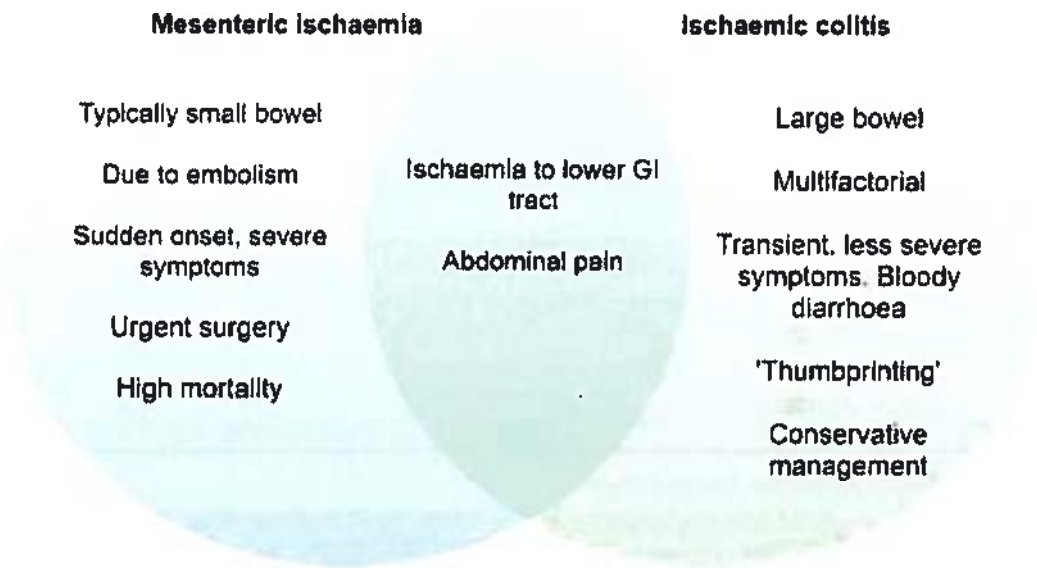
## Functional constipation

- **The Rome criteria for functional constipation is as follows** (it must include two or more of the following):
  - straining during at least 25% of defecations
  - lumpy or hard stools in at least 25% of defecations
  - sensation of incomplete evacuation for at least 25% of defecations
  - sensation of anorectal obstruction/blockage for at least 25% of defecations
  - manual manoeuvres to facilitate at least 25% of defecations (e.g., digital evacuation, support of the pelvic floor)
  - fewer than three defecations per week
  - loose stools are rarely present without the use of laxatives, and
  - insufficient criteria for irritable bowel syndrome.
- These criteria must be fulfilled for the last three months with symptom onset at least six months prior to diagnosis.

# lower gastrointestinal tract Ischaemia

Ischaemia to the lower gastrointestinal tract can result in a variety of clinical conditions. Whilst there is no standard classification it can be useful to separate cases into 3 main conditions

- acute mesenteric ischaemia
- chronic mesenteric ischaemia
- ischaemic colitis




Venn diagram showing types of bowel ischaemia

## Common features in bowel ischaemia

### Common predisposing factors

- increasing age
- atrial fibrillation - particularly for mesenteric ischaemia
- other causes of emboli: endocarditis, malignancy
- cardiovascular disease risk factors: smoking, hypertension, diabetes
- cocaine: ischaemic colitis is sometimes seen in young patients following cocaine use

### Common features

- **abdominal pain** - in acute mesenteric ischaemia this is often of sudden onset, severe and out-of-keeping with physical exam findings
- rectal bleeding

- diarrhoea
- fever
- bloods typically show an elevated white blood cell count associated with a lactic acidosis

## Diagnosis

- CT is the investigation of choice
- **Acute mesenteric ischaemia**
  Acute mesenteric ischaemia is typically caused by an embolism resulting in occlusion of an artery which supplies the small bowel, for example the superior mesenteric artery.
- Classically patients have a history of atrial fibrillation.
- The abdominal pain is typically severe, of sudden onset and out-of-keeping with physical exam findings.

### Management

- urgent surgery is usually required
- poor prognosis, especially if surgery delayed

## Chronic mesenteric ischaemia

- Chronic mesenteric ischaemia is a relatively rare clinical diagnosis due to it's non-specific features and may be thought of as 'intestinal angina'.
- Colickly, intermittent abdominal pain occurs.

## Ischaemiac colitis

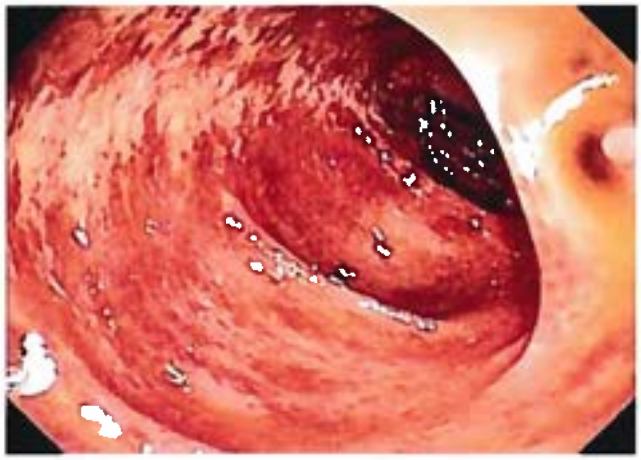
- Ischaemic colitis describes an acute but transient compromise in the blood flow to the large bowel.
- This may lead to inflammation, ulceration and haemorrhage.
- It is more likely to occur in 'watershed' areas such as the splenic flexure that are located at the borders of the territory supplied by the superior and inferior mesenteric arteries.

## Investigations

- 'thumbprinting' may be seen on abdominal x-ray due to mucosal oedema/haemorrhage

## Management

- usually supportive
- surgery may be required in a minority of cases if conservative measures fail.
- Indications would include generalised peritonitis, perforation or ongoing haemorrhage

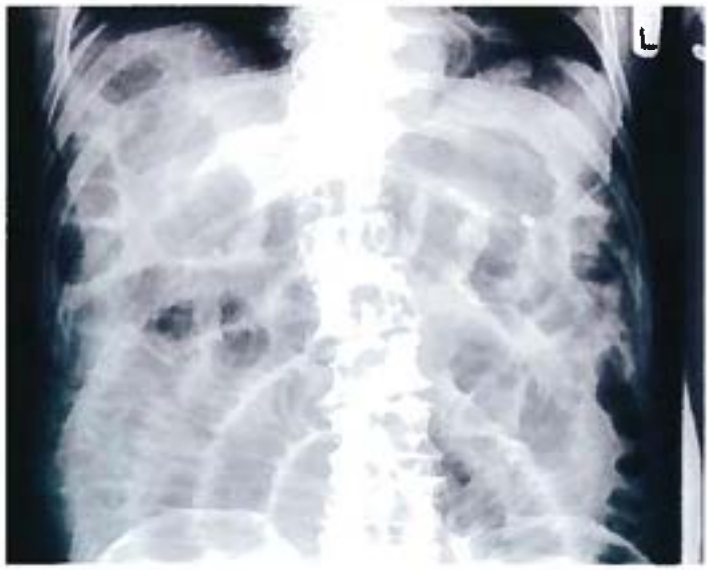


Ischemic colitis in an elderly patient.

## Imaging in bowel obstruction

Looking for small and large bowel obstruction is one of the key indications for performing an abdominal film.

| Small bowel | Large bowel |
|---|---|
| Maximum normal diameter = 35 mm | Maximum normal diameter = 55 mm |
| Valvulae conniventes extend all the way across | Haustra extend about a third of the way across |



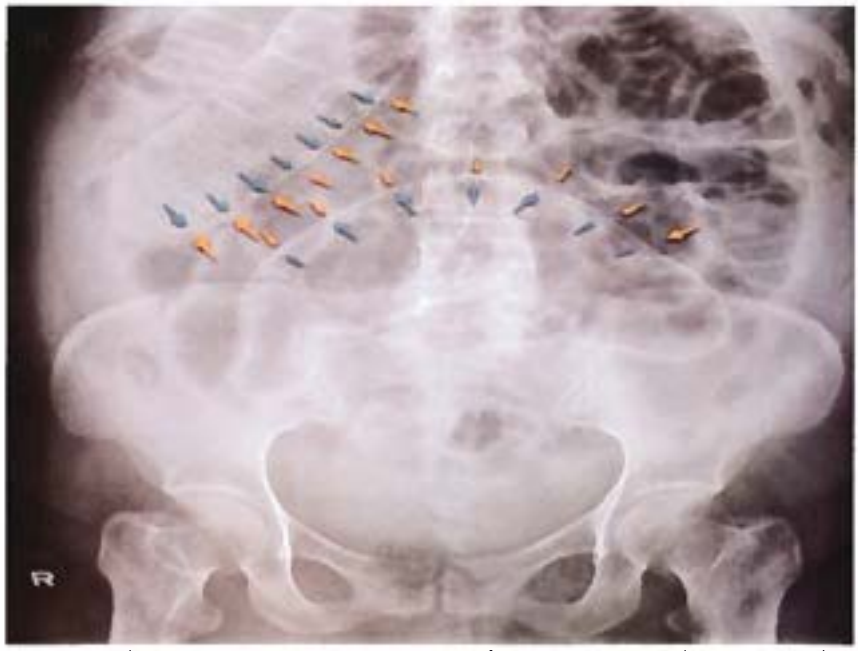
Small bowel obstruction

CT from a patient with small bowel obstruction secondary to adhesions. Distension of small bowel loops proximally (duodenum and jejunum) with abrupt transition to intestinal segment of normal caliber. Presence of small amount of free fluid intracavity.

## Pneumoperitoneum

- An erect chest x-ray is a useful investigation in patients with an acute abdomen as it may demonstrate free air in the abdomen (pneumoperitoneum) - an abnormal finding suggestive of a perforated abdominal viscus (e.g. a perforated duodenal ulcer).
- Rigler's sign (double wall sign) may be seen on an abdominal film.
- CT is now the preferred method for detecting free air in the abdomen.

Erect chest x-ray with air visible under the diaphragm on both sides.



Abdominal x-ray demonstrates numerous loops of small bowel outlined by gas both within the lumen and free within the peritoneal cavity. Ascites is also seen, with mottled gas densities over bilateral paracolic gutters. In a normal x-ray only the luminal surface (blue arrows) should be visible outlined by gas. The serosal surface (orange) should not be visible as it is normally in contact with other intra-abdominal content of similar density (other loops of bowel, omentum, fluid). In this case gas abuts the serosal surface rendering it visible. As this film has been obtained supine (note absence of air-fluid levels), ascites pools in the paracolic gutters, with fluid mixed in with gas bubbles (green arrows).

## Melanosis coli (Surreptitious laxative abuse)

Melanosis coli is a disorder of pigmentation of the bowel wall, dark pigmentation of the colon by colonoscopy.
Histology demonstrates **pigment-laden macrophages.**

It is associated with **laxative abuse**, especially anthraquinone compounds such as **senna**.

It is typically over-represented in **young**, **female** patients and usually closely linked to **eating disorders** (Bulimia and Anorexia) or **psychiatric illness**.

Patients may well present to medical services and be referred on to secondary care with symptoms relating to overuse of laxative agents. They may well also **deny** abusing any medications on initial questioning.

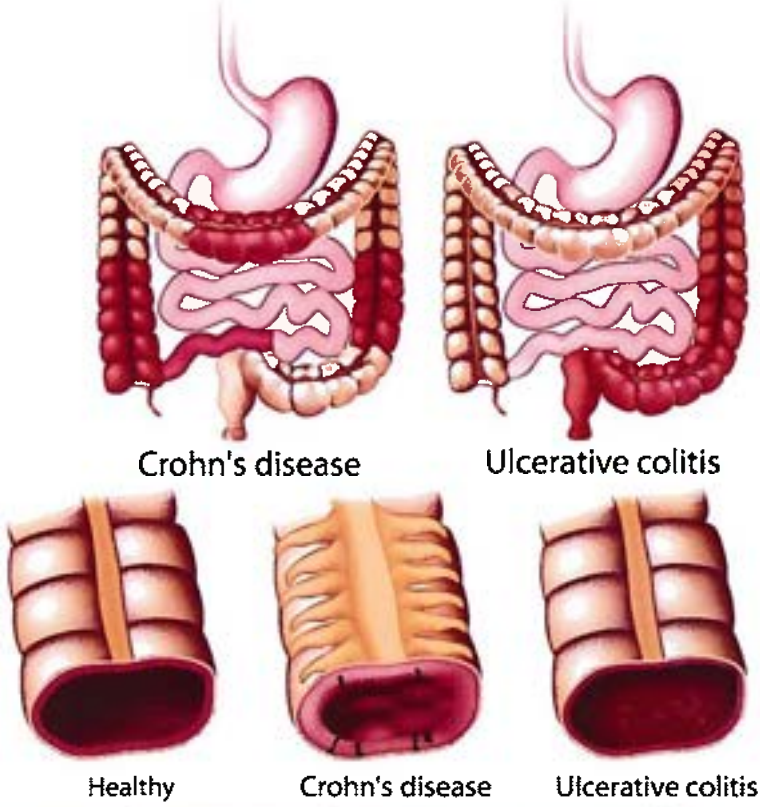
Diarrhoea - biopsy shows pigment laden macrophages = laxative abuse

## Familial Mediterranean Fever

- This is a rare autosomal recessive disorder of unknown pathogenesis that almost exclusively affects people of Mediterranean ancestry, especially Sephardic Jews, Armenians, Turks, and Arabs.
- **Patients lack a protease in serosal fluids that normally inactivates interleukin-8 and the chemotactic complement factor 5A.** Symptoms present in most patients before the age of 20 years.
- It is characterized by episodic bouts of acute peritonitis that may be associated with serositis involving the joints and pleura.
- Peritoneal attacks are marked by the sudden onset of fever, severe abdominal pain, and abdominal tenderness with guarding or rebound tenderness.
- If left untreated, attacks resolve within 24–48 hours.
- Because symptoms resemble those of surgical peritonitis, patients may undergo unnecessary exploratory laparotomy. Colchicine, 0.6 mg orally two or three times daily, has been shown to decrease the frequency and severity of attacks.

# Inflammatory bowel disease (IBD)

Mainly two diseases: **Crohn's disease (CD) and Ulcerative colitis (UC)**




# Crohn's disease (CD)

**Crohn's disease is a form of inflammatory bowel disease.**

- It commonly affects the terminal ileum and colon but may be seen anywhere from the mouth to anus.
- IBD is more common in white people
- People of Jewish origin are more prone to inflammatory bowel disease than non-Jews; and **Ashkenazi Jews are at higher risk than Sephardic Jews.**
- slightly more common in females
- Typically presents in late adolescence or early adulthood.
- The highest incidence of Crohn's disease in the 15–30-year age

## Pathology

- Inflammation occurs in **all layers,** down to the **serosa.** This predisposes to strictures, **fistulas** and adhesions.
- Oedema of mucosa and submucosa, combined with deep **fissured ulcers ('rose-thorn') leads to a 'cobblestone' pattern.**
- Lymphoid aggregates.
- Non-caseating **granulomas.**

## Features

**Crohn's disease typically** presents in late adolescence or early adulthood.

**Features include:**

- presentation may be non-specific symptoms such as **weight loss** and **lethargy**
- **diarrhoea**: the most prominent symptom **in adults**. Crohn's colitis may cause **bloody diarrhoea**
- **abdominal pain**: the most prominent symptom in children
- **perianal disease**: e.g. Skin tags or ulcers
- **extra-intestinal** features are more common in patients with colitis or perianal disease

**Extra-intestinal manifestations of IBD**

- (A PIE SAC):
  - Aphthous ulcers
  - Pyoderma gangrenosum
  - Iritis
  - Erythema nodosum
  - Sclerosing cholangitis
  - Arthritis
  - Clubbing of fingertips
- Arthritis is the most common extra-intestinal feature in both CD and UC
- Episcleritis is more common in CD
- Interstitial lung disease is more common in CD
- Primary sclerosing cholangitis is much more common in UC
- Uveitis is more common in UC

## Smoking in IBD

- Smoking associated with earlier age of onset of disease and more frequent need for immunosuppression **among women** with Crohn's disease **but not men.**
- Smoking cessation is associated with an increased risk of ulcerative colitis.

Questions regarding the 'extra-intestinal' features of inflammatory bowel disease are common:

| | Common to both Crohn's disease (CD) and Ulcerative colitis (UC) | Notes |
|---|---|---|
| **Related to disease activity** | Arthritis: pauciarticular, asymmetric<br>Erythema nodosum<br>Episcleritis<br>Osteoporosis | Arthritis is the most common extra-intestinal feature in both CD and UC<br>Episcleritis is more common in CD |
| **Unrelated to disease activity** | Arthritis: polyarticular, symmetric<br>Uveitis<br>Pyoderma gangrenosum<br>Clubbing<br>Primary sclerosing cholangitis | Primary sclerosing cholangitis is much more common in UC<br>Uveitis is more common in UC |

## Investigation

- C-reactive protein correlates well with disease activity.
- **Nice guidelines 2017 on: monitoring the disease activity by Faecal calprotectin (FC) level at home. And the role of other inflammatory markers**
- It recommends using FC tests in conjunction with clinical symptoms, monitoring and blood tests (C-reactive protein [CRP] and erythrocyte sedimentation rate [ESR]) for distinguishing between inflammatory and non-inflammatory bowel diseases.
- It does not include recommendations on monitoring treatment response. Point-of-care and home fecal calprotectin tests for monitoring treatment response in inflammatory bowel disease After diagnosis, **FC testing can be used to monitor FC levels at check-ups, or in-between if symptoms reoccur.**
    - Calprotectin is a protein and occurring in large amounts in neutrophil granulocytes
    - Increased faecal calprotectin indicates increased migration of neutrophils to intestinal mucosa
    - Calprotectin in stool is the direct consequence of neutrophil degranulation due to mucosal damage.
    - Normal value is approximately 25 mg/kg.
    - in IBD significantly ↑↑ Calprotectin exceeding 50 mg/kg should **be considered positive >> do endoscopy to confirm IBD**

- **Normal faecal calprotectin >> makes IBD unlikely**

  **Stool culture**
  - should be performed first
  - in a case of diarrhoea should be the starting point before considering the other investigations
- anaemia
- low vitamin B12 and vitamin D

## Endoscopy

- colonoscopy is the investigation of choice
- Crohn's disease most typically affects the terminal ileum and proximal colon; therefore, the investigation of choice would be ileo-colonoscopy.
- A flexible sigmoidoscopy may not identify any areas of disease.
- features suggest of Crohn's include deep ulcers, skip lesions

## Histology

- **inflammation in all layers from mucosa to serosa**
- goblet cells
- granulomas
- Patchy inflammation
- Small bowel enema
  - high sensitivity and specificity for examination of the terminal ileum
  - **strictures: 'Kantor's string sign'**
  - proximal bowel dilation
  - **rose thorn' ulcers**
  - Fistulae
- **Thumb printing**
  - is a predominantly radiological finding due to inflamed, oedematous folds of bowel as a result of mucosal oedema caused by inflammation.
  - Thumb printing may be seen in either Crohn's disease or ulcerative colitis

## Advanced level

**Inducing remission in Crohn's disease: 2nd, 3rd lines and severe form (NICE 2019)**

| | Case | Treatment |
|---|---|---|
| **2and line** | • ≥ 2 exacerbations in a 12-month period OR<br>• the glucocorticosteroid dose Cannot be tapered. | Add Azathioprine OR Mercaptopurine to a conventional glucocorticosteroid or budesonide |
| **3rd line** | • Azathioprine or mercaptopurine not tolerated OR<br>• in whom TPMT activity is deficient | add Methotrexate to a conventional glucocorticosteroid or budesonide |
| **Severe form** | very poor general health + one or more symptoms such as weight loss, fever, severe abdominal pain and ≥ 3 diarrhoeal stools daily | • **1st line:** conventional glucocorticosteroids<br>• **2nd line:** (not responded to conventional therapy) (including immunosuppressive and/or corticosteroid treatments) Infliximab or adalimumab |

**Crohn's disease maintaining remission (NICE 2019)**

| | |
|---|---|
| **1st line** | • **Azathioprine OR mercaptopurine**<br>• **Methotrexate only if needed to induce remission** |
| **2nd line** | **Methotrexate** |
| **post-surgery (Complete macroscopic resection)** | • **Azathioprine + in combination with up to 3 months postoperative metronidazole, OR**<br>• **azathioprine alone for people who cannot tolerate metronidazole** |

## General points:

- **patients should be strongly advised to stop smoking**
- Dietary advice
  - **Short-term use of TPN may be helpful in severe cases**
  - There is a significant portion of Crohn's patients who are lactose intolerant, and hence a dairy free diet may reduce the frequency of diarrhea
- some studies suggest an increased risk of relapse secondary to NSAIDs and the combined oral contraceptive pill but the evidence is patchy

## Management

### Inducing remission:

- Glucocorticoids (**oral**, **rectal** or **intravenous**) are generally used to **induce remission**. Budesonide is an alternative in a subgroup of patients. **There is no role of steroids in maintaining remission**.
- **Azathioprine** or **6-mercaptopurine** may be used as **an add-on medication** to induce remission but is not used as monotherapy (check TPMT activity pre usage).
- Methotrexate is an alternative to azathioprine (C.I in anaemia).
- **5-ASA drugs (e.g. mesalazine)** are used **second**-line to glucocorticoids but are **not as** effective as azathioprine.
- Anti TNF therapy (Infliximab IVI):
  - It is a useful biological therapy of Crohn's disease in **refractory** disease, steroids and immunosuppressant-**resistant** and **fistulating** Crohn's disease.
  - It induce a **remission** in **60-80%** of patients.
  - **NICE 2017 recommends** initial induction treatment with infliximab of intravenous infusion at 0, 2 and 6 weeks. No further treatment should be offered if the disease does not respond to this induction treatment. The specialist commentators who contributed to this briefing indicated that current practice would include measurement of infliximab levels in people whose disease has not responded at this point, using a test such as **RIDASCREEN IFX Monitoring.**
  - Allergic reactions are seen in 5% of the cases.
  - It is important to **exclude TB** prior to starting as it can cause reactivation.
  - **Patients typically continue on azathioprine or methotrexate.**
- **Metronidazole is often used for isolated peri-anal disease.**
- Diet in Crohn's:
  - **Short term use of TPN** may be of benefit to allow recovery of calorie intake and improve her weight and nutritional status especially in severely debilitating patients.
  - Enteral feeding with an elemental diet may be used in addition to or instead of other measures to induce remission, particularly if there is concern regarding the side-effects of steroids (for example in young children) (debatable).
  - **Low fat medium chain triglyceride diet** is of benefit especially in patients with significant ileal resection.
  - A significant of Crohn's patients are **lactose intolerant**, so a **dairy free diet** may reduce the frequency of diarrhoea.

### Maintaining remission:

**There is no role of steroids in maintaining remission**

1) **Stopping smoking** is a priority.

Remember: smoking makes Crohn's worse, but may help ulcerative colitis.

2) **Azathioprine** or mercaptopurine is used **first**-line to maintain remission.
3) **Methotrexate** is used **second**-line. (+TPMT activity should be assessed before starting)
4) **5-ASA drugs** (e.g., **mesalazine**) should be considered if a patient has had previous surgery. It is well tolerated but are **not as** effective as azathioprine.

### Surgery:

- Around 80% of pts with Crohn's disease will eventually have surgery.
- Crohn's disease can **recur** following surgery.
- **Loss of the terminal ileum frequently leads to bile salt malabsorption** >>> colonic bile acid irritation leading to >> diarrhoea **(bile acid diarrhoea) (BAD)** with **abnormal 14C glycolate test** >>> **treatment** with the bile salt chelation **cholestyramine** quickly relieves the problem, also this diarrhoea may be due to **short bowel syndrome**.
- Also this ileal resection in Crohn's disease >>> reduce bile salts reabsorption >>> reduce bile salts enterohepatic circulation >>> ↑ increase the risk of **cholesterol gall bladder stones** formation.
- Extensive small bowel resection of Crohn's disease, this predisposes to the formation of **urinary calcium oxalate stones and renal colics** because of changes in the pattern of small bowel flora and electrolyte resorption >>> so ttt good hydration & dietary oxalate restriction (cocoa, peanut products, tea, coffee, wheat germ, rhubarb, beetroot, spinach, tofu and soybeans) and taking cholestyramine to bind bile salts and citrate to prevent stone formation.
- In **Crohn's** disease and after formation of **ileostomy** >>> if develop deep ulcerated areas and begin to form on the skin around the stoma, it is **Pyoderma gangrenosum** >>> treatment: **Oral prednisolone ± topical steroid**.

## Complications:

There are 3 main serious intestinal complications in Crohn's disease:

- Stricture (narrowing) of the bowel >> intestinal obstruction
- Fistulas, which are abnormal connections between sections of the bowel, or between the bowel and bladder.
- Colorectal cancer and small bowel cancer

- Renal calculi are increased in Crohn's due to a mixture of dehydration and increased oxalate due to small bowel pathology and previous surgery.
- Osteoporosis

assess thiopurine methyltransferase (TPMT) activity before offering azathioprine or mercaptopurine

**NB: Lemon juice** ☺ is a natural source of citrate and its consumption by oxalate stone formers can reduce stone formation/growth.

Pt with **Crohn's** disease and underwent **extensive bowel resection** >>> **Diarrhoea** >>> it is due to **Bile acid diarrhoea** or **short bowel syndrome**.

**NB**: The **14C glycolate test** has existed since **1970s** as a way to estimate **bile acid malabsorption** and represents the best test for making the **diagnosis**.

**NB**: Assess thiopurine methyltransferase (TPMT) activity before offering azathioprine (Imuran) or mercaptopurine.

**NB: Diarrhea after cholecystectomy:**
-Bile acid diarrhoea (**BAD**) may affect **10%** of patients following **cholecystectomy**. Typically it is **post-prandial**; the bile, with no gall bladder to store it, is excreted directly into the gut >>> **treatment: Cholestyramine.**
- Also after OR >>> **Antibiotics** >>> **pseudomembranous colitis**.

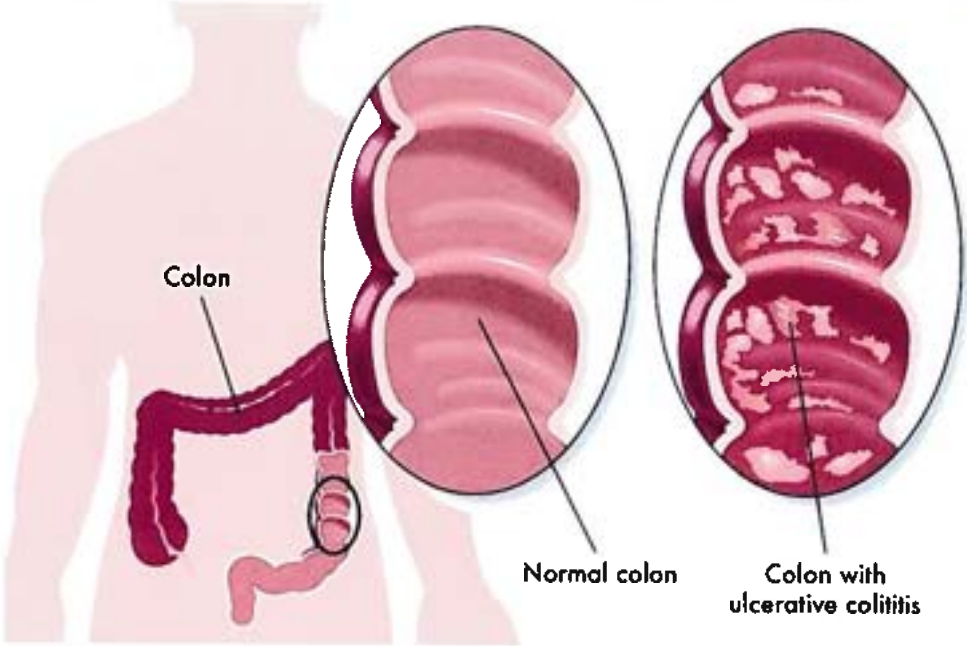
**EX:** female pt. **known to have Crohn's disease**, she has worsening **diarrhoea** especially after taking a course of **Sertraline (Lustral ®)** for depression, **colonoscopy** with biopsy revealed **lymphocytic infiltration** >>> It is **lymphocytic colitis**.

## Ulcerative colitis (UC)

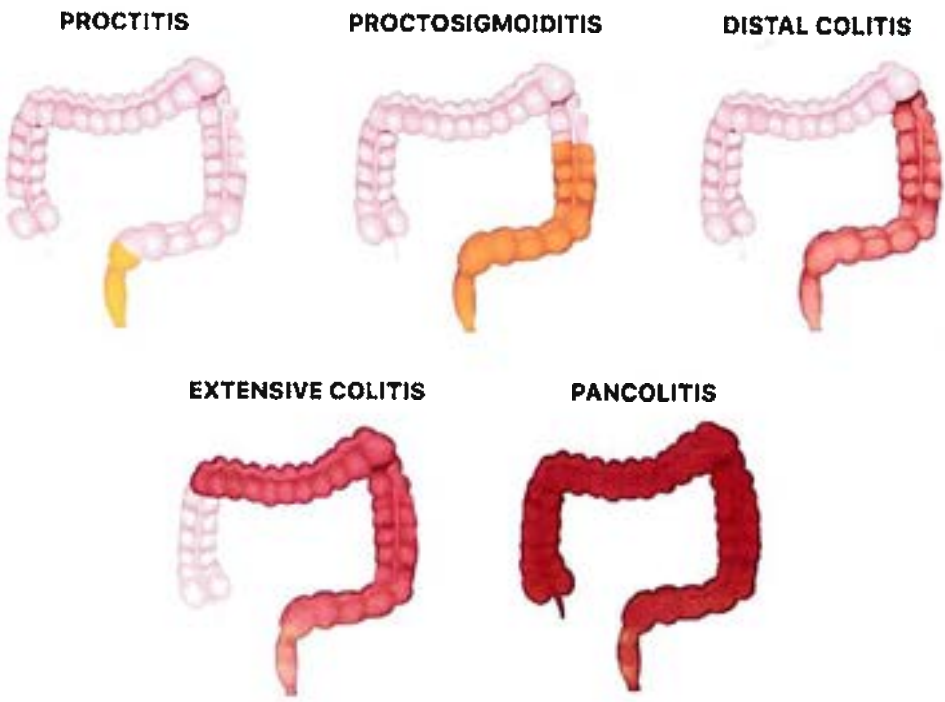
UC is a form of inflammatory bowel disease (IBD).
Inflammation always starts at rectum (hence it is the most common site for UC), never spreads beyond ileocaecal valve and is continuous.

Ulcerative colitis - the **rectum** is the most common site affected

The peak incidence of ulcerative colitis is in people aged 15-25 years and in those aged 55-65 years.




## Types of ulcerative colitis



**The initial presentation is** usually following insidious and intermittent symptoms. Features include:

- **Bloody diarrhoea**
- Urgency
- Tenesmus
- Abdominal pain, particularly in the left lower quadrant
- Extra-intestinal features (see below)

RECURRENT DIARRHEA

ABDOMINAL PAIN & CRAMPING

FATIGUE

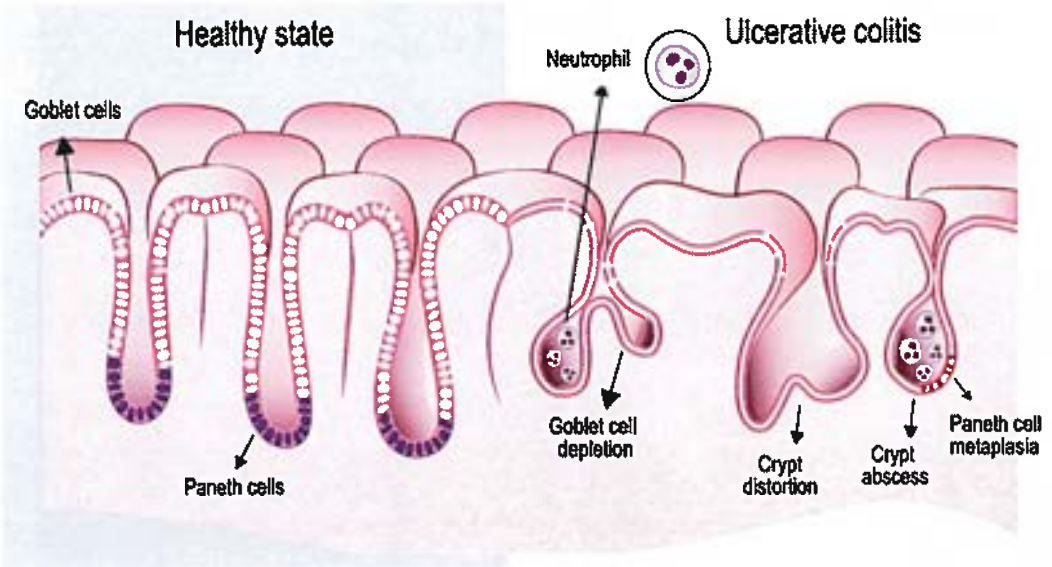
WEIGHT LOSS

BLOOD IN STOOLS

INTESTINAL BLOCKAGE/ SORES/ ULCERS

## Pathology of UC:

- Red, raw mucosa, bleeds easily.
- Inflammation in mucosa and submucosa **only.**
- No inflammation beyond submucosa (unless fulminant disease).
- Widespread ulceration with preservation of adjacent mucosa which has the appearance of polyps **('pseudopolyps').**
- Inflammatory cell infiltrate in lamina propria.
- Neutrophils migrate through the walls of glands to form **crypt abscesses.**
- **Depletion of goblet cells** and mucin from gland epithelium.
- **Granulomas are infrequent.**
- **Inclusion bodies** if present in biopsy this indicate **CMV** infection superimposed on UC >>> **treatment:** Gancyclovir.




## Endoscopy

- colonoscopy + biopsy is generally done for diagnosis
- however in patients with severe colitis colonoscopy should be avoided due to the risk of perforation - a flexible sigmoidoscopy is preferred
- typical findings:
  - red, raw mucosa, bleeds easily
  - **no inflammation beyond submucosa** (unless fulminant disease)
  - widespread ulceration with preservation of adjacent mucosa which has the appearance of polyps **('pseudopolyps')**
  - inflammatory cell infiltrate in lamina propria
  - neutrophils migrate through the walls of glands to form **crypt abscesses**
  - **depletion of goblet cells** and mucin from gland epithelium
  - granulomas are infrequent

## Barium enema:

- **Loss of haustrations**
- Superficial ulceration, **'pseudopolyps'**
- Long standing disease: colon is narrow and short -**'drainpipe colon'**

**Questions regarding the 'extra-intestinal' features of inflammatory bowel disease are common:**

Barium enema from a patient with ulcerative colitis. The whole colon, without skips is affected by an irregular mucosa with loss of normal haustral markings.

Abdominal x-ray from a patient with ulcerative colitis showing lead pipe appearance of the colon (red arrows). Ankylosis of the left sacroiliac joint and partial ankylosis on the right (yellow arrow), reinforcing the link with sacroiliitis.

## Ulcerative colitis: flares

Most ulcerative colitis flares occur without an identifiable trigger. However, a number of factors are often linked:

- stress
- medications
  - NSAIDs
  - antibiotics
- **cessation of smoking**

Flares of ulcerative colitis are usually classified as either mild, moderate or severe:

| Mild | Moderate | Severe |
|---|---|---|
| Fewer than four stools daily, with or without blood<br><br>No systemic disturbance<br><br>Normal erythrocyte sedimentation rate and C-reactive protein values | Four to six stools a day, with minimal systemic disturbance | More than six stools a day, containing blood<br>Evidence of systemic disturbance, e.g.<br>• fever<br>• tachycardia<br>• abdominal tenderness, distension or reduced bowel sounds<br>• anaemia<br>• hypoalbuminaemia |

Patients with evidence of severe disease should be admitted to hospital.

## Management: (Nice guidelines 2019)

### 1. Proctitis:

- To induce remission, offer **a topical aminosalicylate** as first line treatment.
  - If remission is not achieved within 4 weeks, consider adding an **oral aminosalicylate.**
  - For people who cannot tolerate aminosalicylates, consider a time-limited course of **a topical or an oral corticosteroid.**

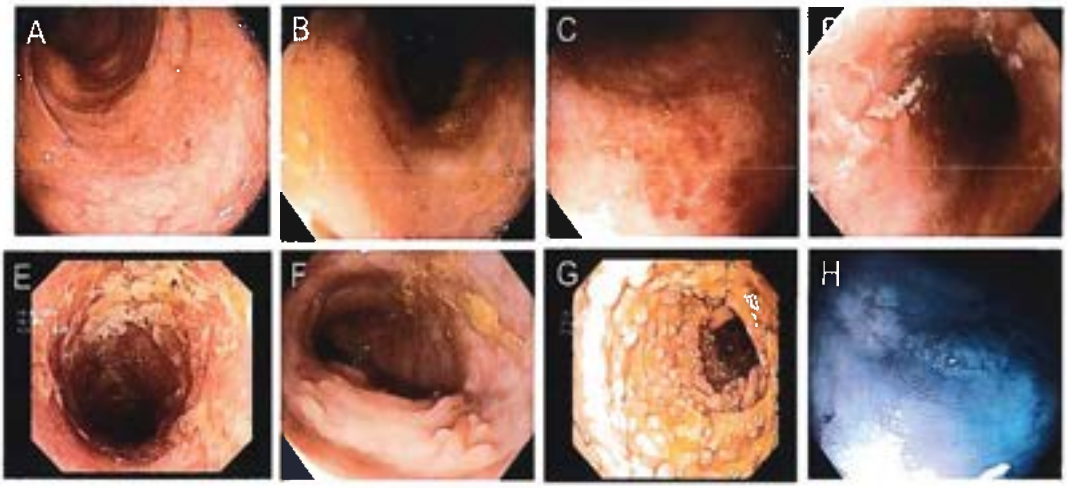
### 2. Proctosigmoiditis and left-sided ulcerative colitis:

- To induce remission, offer a **topical aminosalicylate** as first-line treatment.
  - If remission is not achieved within 4 weeks, consider:
  - adding **a high-dose oral aminosalicylate** to the topical aminosalicylate or
  - switching to a **high-dose oral aminosalicylate and a time-limited course of a topical corticosteroid.**

### 3. Extensive disease:

- To induce remission in people with a mild-to-moderate first presentation or inflammatory exacerbation of extensive ulcerative colitis, **offer a topical aminosalicylate and a high-dose oral aminosalicylate as first-line treatment.**
  - If remission is not achieved within 4 weeks, **stop the topical aminosalicylate and offer a high-dose oral aminosalicylate** with a time-limited course of an **oral corticosteroid.**
  - For people who cannot tolerate aminosalicylates, consider a time-limited course of an oral corticosteroid. [2019]

**Ulcerative colitis endoscopy images**




A. Mild disease with erythema and decreased vascular pattern consistent with Mayo score of 1. B. Moderate disease with Loss of vascular pattern and erosions consistent with Mayo score of 2. C. Erythematous mucosa. erosions and absent vascular pattern consistent with Mayo score of 2. D. Severe disease with deep ulcerations demonstrative of Mayo score of 3. E. Severe diffuse ulcerations consistent with Mayo score of 3. F. Scattered pseudopolyps in inactive ulcerative colitis. G. Dense pseudopolyps making dysplasia surveillance difficult H. Chromoendoscopy following application of dye spray demonstrating dysplastic lesion.

# Ulcerative colitis: colorectal cancer

## Overview:

- Risk of colorectal cancer is **10-20 times** that of general population
- This increased risk is mainly related to **chronic inflammation.**
- Worse prognosis than patients without ulcerative colitis (partly due to delayed diagnosis)
- Lesions may be multifocal
- On **endoscopy**, **mucosal dysplasia** seen on rectal biopsy
- **Endoscopy** not CEA is a useful **screening** test of **cancer**.
- CEA is a marker of disease response to ttt, CEA may not be elevated in early stage of cancer

## Factors increasing risk of cancer:

- Disease **duration > 10 years**
- **Onset before 15 years old**
- Patients with **pancolitis**
- **Unremitting** disease
- Poor **compliance** to treatment

## Colonoscopy surveillance & Risk stratification of IBD

- **Patients should be decided following risk stratification.**

### Lower risk

**5 years follow up colonoscopy**

- Extensive colitis with no active endoscopic/histological inflammation
- left sided colitis
- Crohn's colitis of <50% colon

### Intermediate risk

**3-year colonoscopy**

- Extensive colitis with mild active endoscopy/histological inflammation
- post-inflammatory polyps
- family history of colorectal cancer in a first degree relative aged 50 or over

### Higher risk

**1 year follow up colonoscopy**

- Extensive colitis with moderate/severe active endoscopic/histological inflammation
- stricture in past 5 years
- dysplasia in past 5 years declining surgery
- primary sclerosing cholangitis / transplant for primary sclerosing cholangitis
- family history of colorectal cancer in first degree relatives aged <50 years

## Toxic megacolon

- It is a severe colitis (**pancolitis**).
- It is defined as **dilatation of the transverse colon ≥ 6 cm at its widest point radiologically on abdominal x ray or CT**.
- If there is a delay in surgery toxic dilatation of the colon carries the risk of **perforation** which has a high mortality.
- It most often occurs in the context of **ulcerative** colitis, but can also occur in CD, pseudomembranous colitis, ischaemic colitis and other colitides.
- **Truelove-Witts Criteria of severe colitis:**
  1) **More than 6 bloody diarrhoea / day**
  2) **Temperature > 37.8 °C in 2 out of 4 days.**
  3) **HR > 90 bpm.**
  4) **TLC:** Neutrophil count greater than 10 ×109/L
  5) **Hb < 10.5 gm/dl**
  6) **ESR > 30 mm/hr**

7) **CRP > 30 mg/L**
8) **Dilated colon ≥ 6 cm**
9) **Other** radiological findings include loss of haustral pattern, mucosal oedema and thumb printing.

- It is an **absolute contraindication** to **Ba** enema examination because of the risk of bowel perforation.
- High mortality about 20%.
- European Crohn's and Colitis Organisation consensus guidelines on the management of ulcerative colitis identify the following as **risk factors for the precipitation of toxic colonic dilatation:**
  - Hypokalaemia
  - **Hypomagnesaemia**
  - Under-treatment
  - Purgative bowel preparations for colonoscopy
  - NSAIDs
  - Opioids
  - Anti-cholinergics, and
  - Anti-diarrhoeal agents.
- **treatment:** in **HDU** (high dependency unit): **High dose of IV steroids + Rectal steroids + IV fluids + LMWL ± Cyclosporine ± Infliximab ± surgery (colectomy).**
- Antibiotics have not been demonstrated of help.

Toxic megacolon

**Severe colitis >>>> IV Fluids + IV steroids (Hydrocortisone)**

**High relapse rate for UC**, with **75%** of medically treated patients eventually suffering a relapse.

## Lymphocytic colitis

It may occur in patients **with other forms of GIT pathology** including **Crohn's** and **Coeliac**.

**Sertraline** (**Lustral ®**) also appears to be associated with the development of Lymphocytic colitis.

### Treatment:

- Withdrawal of the offending agent is preferable.
- Loperamide.
- Cholestyramine.
- Azathioprine (although the response to ttt may take many years).
- About 20% of patients have a spontaneous remission.

## Microscopic colitis

It is defined by the triad of

- **Watery diarrhoea**
- **Normal colonoscopy**
- Increased **cellular** inflammation at **lamina propria**

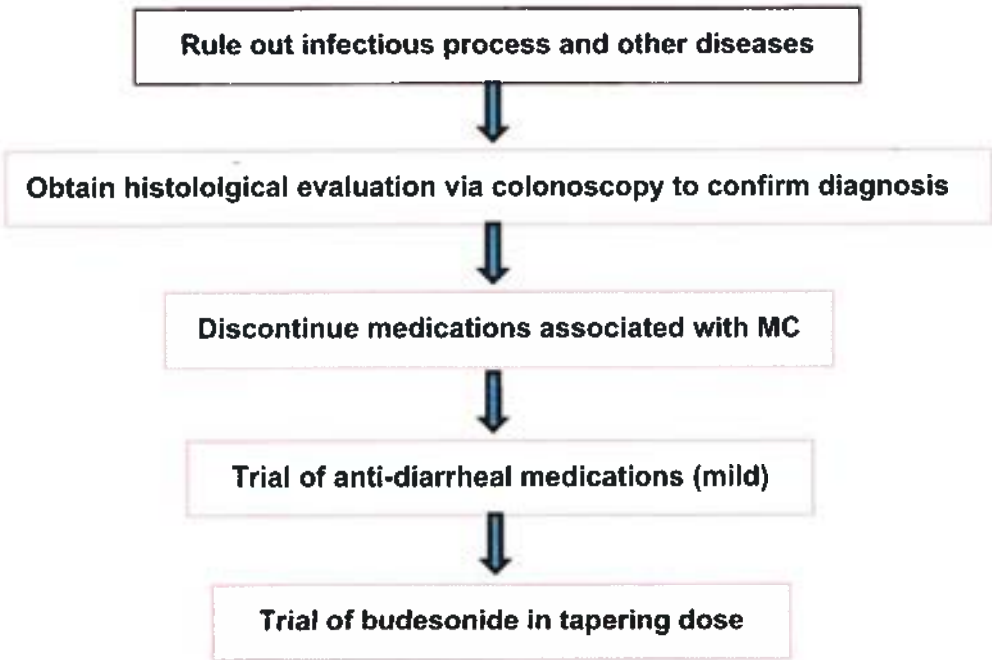
It is a **histological diagnosis** with **macroscopically normal colon mucosa**.

It is an uncommon disease with an incidence of 5/100,000 per year and frequents **older** patients (mean age **55-65**) and **women**.

There is a **link** with **NSAIDs**, **H2 blocker** and **PPI**.

### Treatment:

- **Stopping** the offending medications.
- Corticosteroids, azathioprine, cholestyramine and now bismuth have been used as a treatment with some effects in patients who did not respond adequately to cessation of the causative agent.


Rule out infectious process and other diseases
Obtain histololgical evaluation via colonoscopy to confirm diagnosis
Discontinue medications associated with MC
Trial of anti-diarrheal medications (mild)
Trial of budesonide in tapering dose

## Diverticulosis

Diverticulosis is an extremely common disorder characterised by multiple outpouchings of the bowel wall, most commonly in the sigmoid colon. Strictly speaking the term diverticular disease is reserved for patients who are symptomatic - diverticulosis is the more accurate term for diverticula being present.

### Risk factors

- increasing age
- low-fibre diet

### Diverticulosis can present in a number of ways:

- painful diverticular disease: altered bowel habit, colicky left sided abdominal pain. A high fibre diet is usually recommended to minimise symptoms
- diverticulitis: see below for more details

## Diverticulitis

One of the diverticular become infected. The classical presentation is:

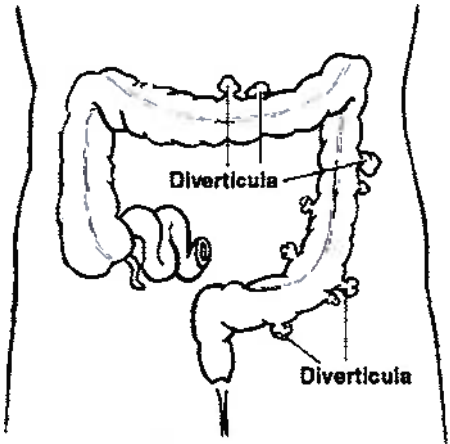
- left iliac fossa pain and tenderness
- anorexia, nausea and vomiting
- diarrhoea
- features of infection (pyrexia, raised WBC and CRP)

## Management:

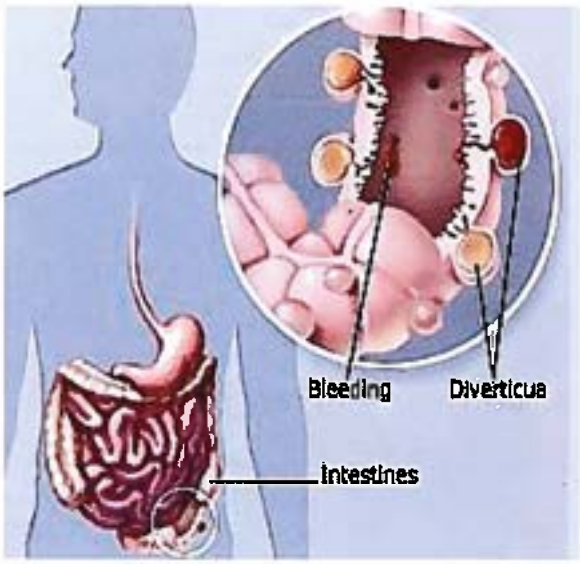
- mild attacks can be treated with oral antibiotics
- more significant episodes are managed in hospital. Patients are made nil by mouth, intravenous fluids and intravenous antibiotics (typical a cephalosporin + metronidazole) are given

## Complications of diverticulitis include:

- abscess formation
- peritonitis
- obstruction
- perforation




Colon with several diverticula



# Aminosalicylate drugs

5-aminosalicyclic acid (5-ASA) is released in the colon and is not absorbed. It acts locally as an anti-inflammatory. The mechanism of action is not fully understood but 5-ASA may inhibit prostaglandin synthesis

## Sulphasalazine:

- a combination of sulphapyridine (a sulphonamide) and 5-ASA
- many side-effects are due to the sulphapyridine moiety: **rashes, oligospermia, headache, Heinz body anaemia, megaloblastic anaemia, lung fibrosis**
- other side-effects are common to 5-ASA drugs (see mesalazine)

## Mesalazine

- a delayed release form of 5-ASA
- sulphapyridine side-effects seen in patients taking sulphasalazine are avoided
- mesalazine is still however associated with side-effects such as GI upset, headache, agranulocytosis, pancreatitis*, interstitial nephritis

## Olsalazine

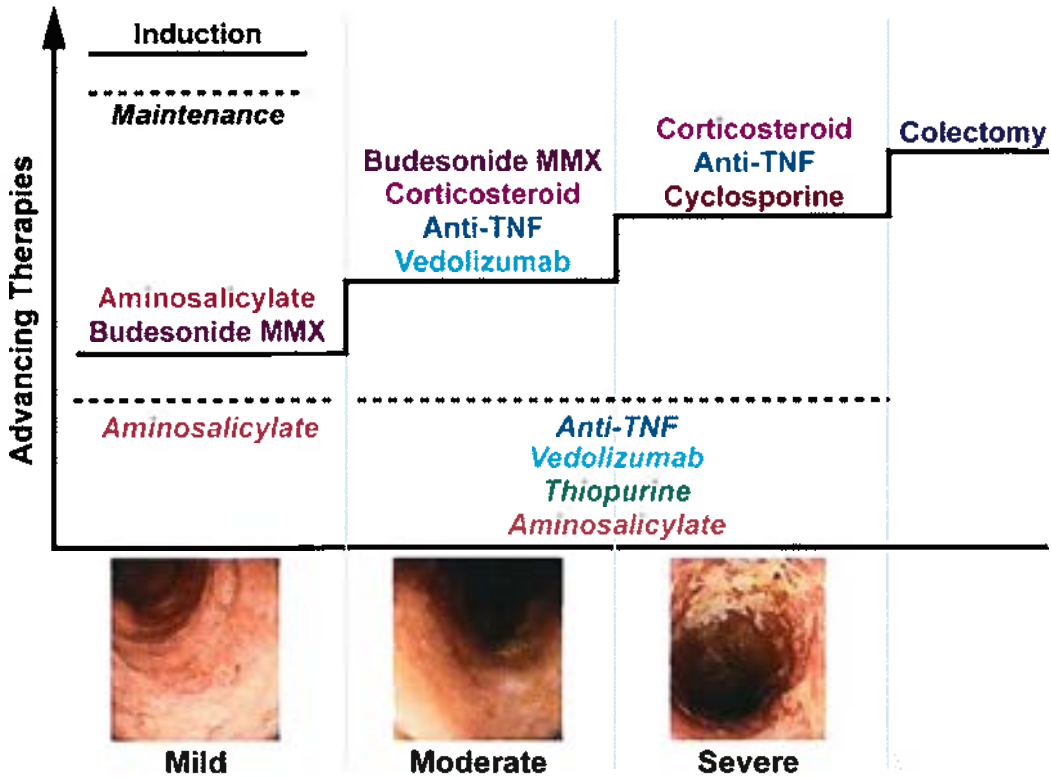
- two molecules of 5-ASA linked by a diazo bond, which is broken by colonic bacteria

Aminosalicylates are associated with a variety of haematological adverse effects, including agranulocytosis - FBC is a key investigation in an unwell patient taking them.

pancreatitis is 7 times more common in patients taking mesalazine than sulfasalazine

Ozanimod and upadactinib evidence for use in ulcerative colitis and nice recommendations expected to be published late in 2022 and 2023.

**EX**: Patient known to have **ulcerative colitis** on **prednisolone** 10 mg OD and **azathioprine** 50 mg OD, then he develops **acute severe epigastric pain** >>> **drug-induced acute pancreatitis** (**azathioprine**) due to **idiosyncratic** response, it has a good prognosis.
A high index of suspicion and careful drug history are essential for diagnosis.

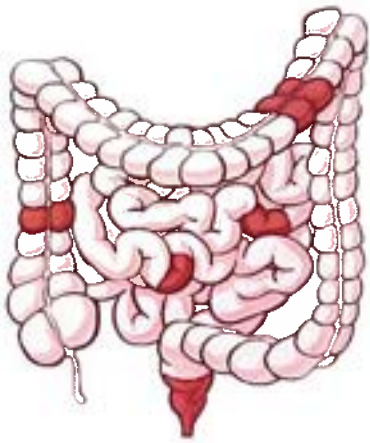



Step-up approach to treatment based on disease severity.
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(16)32126-2/fulltext

## key differences between different types of IBD

They have many similarities in terms of presenting symptoms, investigation findings and management options. There are however some key differences which are highlighted in table below:

| | Crohn's disease (CD) | Ulcerative colitis (UC) |
|---|---|---|
| **Features** | • Diarrhoea usually non-bloody.<br>• **Weight loss** more prominent.<br>• **Upper** GI symptoms, **mouth ulcers.**<br>• **Perianal** disease.<br>• Abdominal mass palpable in the **right iliac fossa.** | • **Bloody** diarrhoea more common.<br>• **Tenesmus.**<br>• Abdominal pain in the **left lower** quadrant. |

| | | |
|---|---|---|
| **Extra-intestinal** | **Gallstones** are more common secondary to reduced bile acid reabsorption.<br>**Oxalate renal stones.** | **Primary sclerosing cholangitis (PSC)** more common |
| **Complications** | Obstruction, **fistula, anal tags,** colorectal cancer. | Risk of **colorectal cancer high** in UC than CD. |
| **Pathology** | Lesions may be seen anywhere from the mouth to anus.<br>Skip lesions may be present.<br>  | Inflammation always starts at rectum and never spreads beyond ileocaecal valve.<br>Continuous disease.<br> |
| **Histology** | Inflammation in **all** layers from mucosa to serosa<br>• **increased goblet cells**<br>• **Granulomas.** | No inflammation beyond submucosa (unless fulminant disease) - inflammatory cell infiltrate in lamina propria<br>• Neutrophils migrate through the walls of glands to form **crypt abscesses.**<br>• **Depletion of goblet cells** and mucin from gland epithelium.<br>• **No Granulomas are infrequent.** |

<table>
<tr>
<td>Endoscopy</td>
<td>
• Deep ulcers,<br>
• Skip lesions,<br>
• 'Cobble-stone' appearance.<br>

</td>
<td>
Widespread ulceration with preservation of adjacent mucosa which has the appearance of polyps ('pseudopolyps')<br>

</td>
</tr>
<tr>
<td>Radiology</td>
<td>
Small bowel enema<br>
• High sensitivity and specificity for examination of the terminal ileum.<br>
• Strictures: 'Kantor's string sign'.<br>
<br>
• Proximal bowel dilation.<br>
• 'Rose thorn' ulcers.<br>

<br>
• Fistulae (e.g., Colo-vesical)
</td>
<td>
Barium enema<br>
• Loss of haustrations<br>
• Superficial ulceration, 'pseudopolyps'<br>
• Long standing disease: colon is narrow and short -'drainpipe colon'<br>

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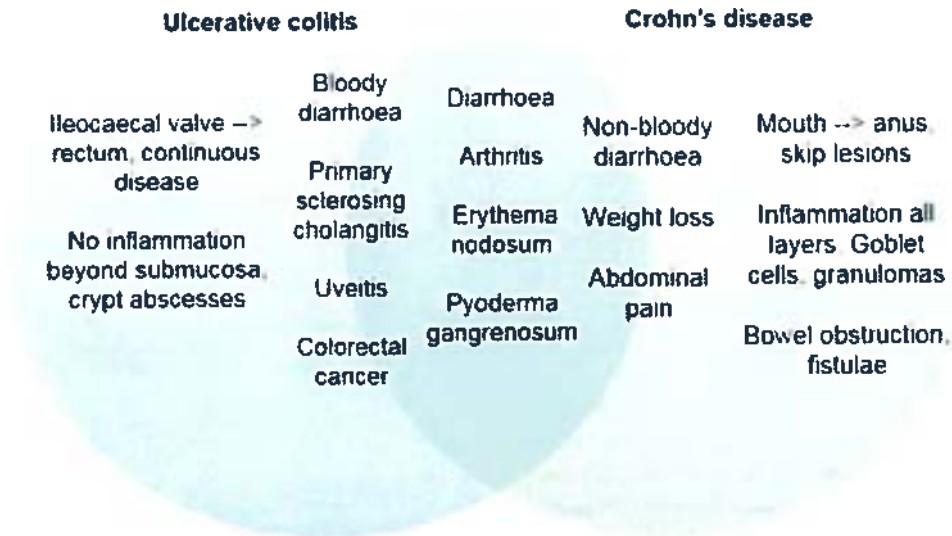



Venn diagram showing shared features and differences between ulcerative colitis and Crohn's disease. Note that whilst some features are present in both, some are much more common in one of the conditions, for example colorectal cancer in ulcerative colitis

Barium study is shown from a patient with worsening Crohn's disease. Long segment of narrowed terminal ileum in a 'string like' configuration in keeping with a long stricture segment. Termed 'Kantor's string sign'.

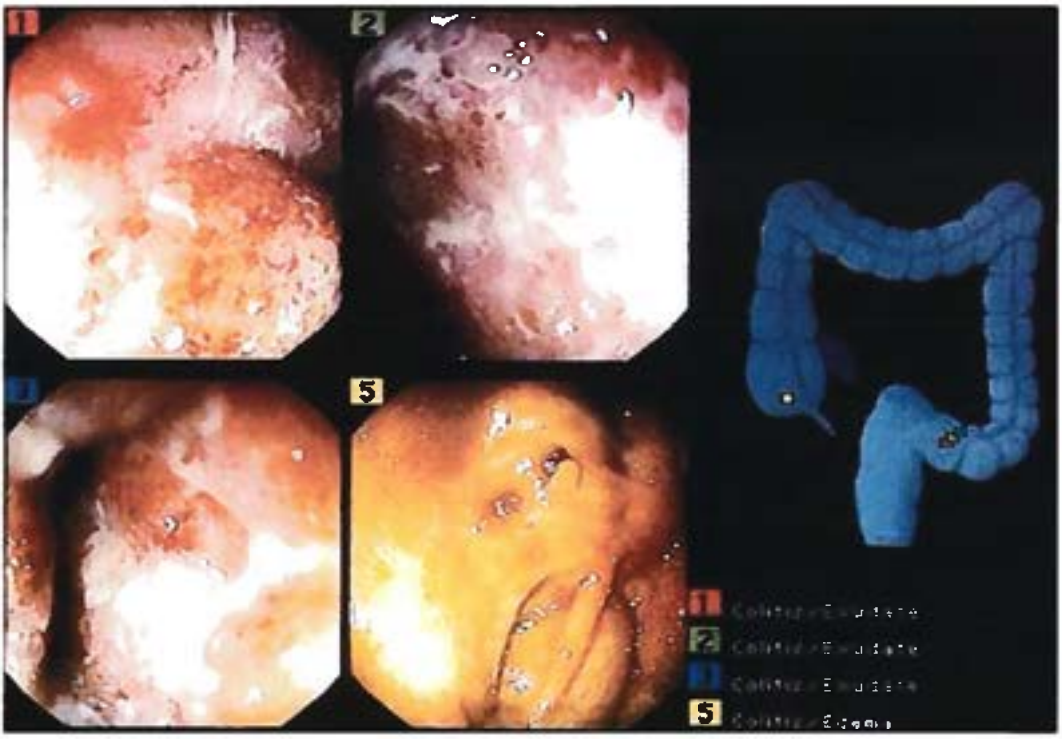
Abdominal x-ray from a patient with ulcerative colitis showing lead pipe appearance of the colon (red arrows). Ankylosis of the left sacroiliac joint and partial ankylosis on the right (yellow arrow), reinforcing the link with sacroilitis.

*Impaired bile acid reabsorption increases the loss calcium in the bile. Calcium normally binds oxalate.

**NB**: **Pseudopolyps** are seen in **both** ulcerative colitis and Crohn's disease.

**NB**: Causes of GI fistulae: Crohn's, diverticulitis and colorectal tumours.

**NB**: Diagnosis of IBD is mainly based on **clinical history**, **inflammatory markers**, **and colonoscopy & histology results**.
In around 10% of patients, it is impossible to distinguish CD from UC and this is termed an **indeterminate colitis**.



Endoscopic image showing friability and exudates over superficial ulceration in the sigmoid colon. There is edema in the cecum that, all together, indicates pancolitis. Biopsy confirmed ulcerative colitis

Pseudopolyps in "active" ulcerative colitis viewed through colonoscope

Crohn colitis with deep longitudinal ulcers and normal-appearing tissue between. The biopsies that showed normal tissue between the ulcers clinched the diagnosis for Crohn disease. Ulcerative colitis is diffuse, whereas CD often skips areas as seen in this patient's colon.

## Dysplastic colonic polyps

Guidelines on the follow-up period for dysplastic colonic polyps:

- 5-year interval is indicated for low-risk patients (one to two adenomas that are both small, ie <1 cm)
- **3-year follow up is recommended for medium-risk patients (three to four adenomas or one or two adenomas where one adenoma bigger than or equal to 1 cm)**
- 1-year follow-up is recommended for high-risk patients (five or more small adenomas or more than three with at least one at or above 1 cm in size).

**Polyp characteristics**:

Associated with a **higher risk of malignant change:**

- **polyps greater than 1.5 cm, which are sessile or flat**
- Histology demonstrating severe dysplasia, predominantly villous architecture or squamous metaplasia

## Villous adenoma

### Overview

- Villous adenomas are colonic polyps with the potential for malignant transformation.
- They **characteristically secrete large amounts of mucous**, potentially resulting in electrolyte disturbances.

**Features**: The vast majority are asymptomatic.

**Possible features:**

- non-specific lower gastrointestinal symptoms
- secretory diarrhoea may occur
- microcytic anaemia
- hypokalaemia

## Peutz-Jeghers syndrome (PJS)

- Peutz-Jeghers syndrome is an **autosomal dominant** condition caused by a germline **mutation** of the **STK11** (serine threonine kinase 11) gene, usually located on the long arm of chromosome **19**.
- PJS is characterised by **numerous hamartomatous polyps** in the gastrointestinal tract (stomach and large intestine).
- The polyps only rarely undergo malignant change.
- It is also associated with **pigmented freckles** on the lips, face, palms, soles and perianal skin. It is usually (90%) associated with **peri-oral pigmentation**.
- Around **50%** of patients will have **died** from a **GIT cancer** by the age of **60** years.
- **Colon cancer** is the **most common** type of gastrointestinal cancer that patients with Peutz-Jeghers syndrome develop.
- There is an association with non-GIT malignancies like endometrial, ovarian & lung.

### Genetics:

- Autosomal dominant (AD)
- **Responsible gene encodes serine threonine kinase LKB1 or STK11**

### Features:

- **Hamartomatous polyps in GI tract** (mainly small bowel)
- **Mucocutaneous melanocytic macules**: Pigmented lesions on lips, oral mucosa, face, palms and soles
- Intestinal **obstruction** e.g. **intussusception**
- Gastrointestinal **bleeding** >>> **Fe Def. Anemia**.

### Management:

- Conservative unless complications develop

Pts with Peutz-Jeghers syndrome require **colonoscopy** ***every 2 years*** after the age of 25 years for evaluation of the presence of polyps and polypectomy.

**NB**: **Osteomas** are a feature of **Gardner's** syndrome, a variant of familial adenomatous polyposis (FAP), **not** present in Peutz-Jeghers syndrome.

Defective mismatch repair genes **hMSH2** and **hMLH1** leads to hereditary non-polyposis colorectal cancer (**HNPCC**).
Mutation of **APC** gene leads to familial adenomatous polyposis (**FAP**).
Mutation of **STK11/LKB1** gene is with Peutz-Jeghers syndrome (**PJS**)

## Angiodysplasia

Angiodysplasia is a **vascular** deformity of the gastrointestinal tract which predisposes to bleeding and iron deficiency anaemia.

Angiodysplasia is generally seen in **elderly** patients.

There is thought to be **an association with** aortic stenosis, although this is debated.

It may be found **throughout** the GIT, although it most commonly occurs in the **caecum** and **ascending colon**.

It is a significant cause of **chronic** anaemia and can also cause **acute** haemorrhage.

### Diagnosis:

- **Colonoscopy.**
- **Capsule endoscopy**
- Mesenteric angiography if acutely bleeding.

**Management:**

- Endoscopic **cautery** or **argon plasma photo coagulation (APPC).**
- **Embolisation** of the bleeding vessel during **angiography**.
- **Surgical resection.**
- Antifibrinolytics e.g. Tranexamic acid.
- Oestrogens may also be used.

**EX**: A 67-year-old man presents with shortness-of-breath. He has a past history of **aortic stenosis** but is otherwise well. On examination he has a systolic murmur and a clear chest. Routine bloods shows: **Hb 8.7 gm%, low MCV** >>> this patient most likely has **angiodysplasia** which has a known association with aortic stenosis >>for **colonoscopy**.

**EX**: Old male 66 years old with bleeding per rectum and Hb is 8 gm%, gastroscopy and Ba enema are normal >>>?? **Angiodysplasia** >>> **Capsule enteroscopy** or **Mesenteric angiography**: **abnormal vascular blush in the ascending colon**.
After **diverticulosis**, **angiodysplasia** is the second leading cause of **lower** GI bleeding in patients **older than 60 years**.

## Intussusception

- Hirschsprung disease is aganglionosis of colon, causing obstruction. It usually presents in neonatal period.
- common cause of intestinal obstruction in children in general and in Down's syndrome in particular.
- There is a classic triad in intussusception of:
  - acute abdominal pain,
  - currant jelly stool and
  - palpable abdominal mass, usually in right iliac fossa.

## Aorto-enteric fistulae (AEF)

known to occur following endovascular repair of abdominal aortic aneurysms (AAA) and secondary to aortic grafting of any kind, presumably because of mechanical forces of dislodged or migrating devices.

May occur after aorto-bifemoral graft as treatment for peripheral vascular disease.

**Strongly positive faecal occult blood (FOB) suggests significant GI haemorrhage in spite of normal upper GI endoscopy.**

# Colorectal cancer

Colorectal cancer is the third most common type of cancer in the UK and the second most cause of cancer deaths.

## Location of cancer (averages)

- rectal: 40%
- sigmoid: 30%
- descending colon: 5%
- transverse colon: 10%
- ascending colon and caecum: 15%

## Genetics

**It is currently thought there are three types of colon cancer:**

- sporadic (95%).
- hereditary non-polyposis colorectal carcinoma (HNPCC, 5%).
- familial adenomatous polyposis (FAP, <1%).

**Studies have shown that sporadic colon cancer**

- may be due to a series of genetic mutations. For example
- allelic loss of the APC gene. (more than half of colon cancers)
- further series of gene abnormalities e.g.
- activation of the K-Ras oncogene,
    - RAS is an intracellular signalling molecular that acts downstream of the epidermal growth factor receptor (EGFR) to stimulate cell division and growth
    - present in 30-50% of colorectal cancers
    - associated with failure to respond to (EGFR) based therapies such as the monoclonal antibodies (**Cetuximab** and Panitumumab)
    - **The presence of a KRAS mutation is a contraindication to treatment with these agents.**
- deletion of p53 and DCC tumor suppressor genes lead to invasive carcinoma.

**Hereditary non-polyposis colorectal carcinoma (HNPCC) (Lynch syndrome),** an autosomal dominant condition,

- Most common form of inherited colon cancer.
- Around 90% of patients develop cancers, often of the proximal colon, which are usually poorly differentiated and highly aggressive.
- Currently seven mutations have been identified, which affect genes involved in DNA mismatch repair leading to microsatellite instability.
- The most common genes involved are:

- **MSH2 (60% of cases)**
- **MLH1 (30%)**

Patients with HNPCC are also at a higher risk of other cancers, with endometrial cancer being the next most common association, after colon cancer.

**The Amsterdam criteria are sometimes used to aid diagnosis:**

- at least 3 family members with colon cancer
- the cases span at least two generations
- at least one case diagnosed before the age of 50 years

**Torre-Muir syndrome**

- A type of hereditary nonpolyposis colorectal cancer (HNPCC), is **characterized by sebaceous adenomas.**
- These lesions are usually present on the face, near the eyes and forehead and appear as yellow papules/nodules.

**Familial adenomatous polyposis (FAP)** is a rare autosomal dominant condition which leads to the formation of hundreds of polyps

- by the age of 30-40 years.
- Patients inevitably develop carcinoma.
- It is due to a mutation in a tumor suppressor gene **called adenomatous polyposis coli gene (APC),** located on chromosome 5.

- Genetic testing can be done by analyzing DNA from a patient's white blood cells.
- Patients generally have a total colectomy with ileo-anal pouch formation in their twenties.
  Patients with FAP are also at risk from duodenal tumors.
- A variant of FAP called **Gardner's syndrome** can also feature

**Gardner's syndrome**

- osteomas of the skull and mandible,
- retinal pigmentation,
- thyroid carcinoma
- epidermoid cysts on the skin
- Multiple lipomas, fibromas
- It carries an increased risk of papillary carcinoma of the thyroid
- Colonic carcinoma develops in 7% of individuals by age 21 years, 50% by age 39 years and 90% by age 45 years.
- Colectomy is recommended once polyps appear.

## The Dukes' System staging

**It is classified as following:**

**Dukes' A:**

Invasion into but not through the bowel wall,
80% + 5-year survival

- Follow-up of a Dukes' A colon cancer
- **Colonoscopy - indicated on an annual basis for the first 2 years, then this should be done 3-yearly**
- Faecal occult blood - should be tested 6-monthly for the first 4 years and then once yearly
- Carcinoembryonic antigen (CEA) - can be used to monitor for recurrence if it is elevated initially

**Dukes' B:**

- Invasion through the bowel wall but not involving lymph nodes
- 60-70% 5-year survival

**Dukes' C:**

- Involvement of lymph nodes,
- **30-40% 5-year survival**

**Dukes' D**

- Widespread metastases
- 0% 5-year survival

# Colorectal cancer: screening

## Overview

- most cancers develop from adenomatous polyps. Screening for colorectal cancer has been shown to reduce mortality by 16%
- the NHS offers home-based, **Faecal Immunochemical Test (FIT)** screening to older adults
- **a one-off flexible sigmoidoscopy at the age of 55 years was trailed in England but was abandoned in 2021**
  - this mainly due to an inability to recruit enough clinical endoscopist, exacerbated by the covid-19 pandemic
  - the trial, partly funded by Cancer Research UK, had shown promising early results and it remains to be seen whether flexible sigmoidoscopy will be used as part of a future bowel screening program.

## At colonoscopy, approximately:

- 5 out of 10 patients will have a normal exam
- 4 out of 10 patients will be found to have polyps which may be removed due to their premalignant potential
- 1 out of 10 patients will be found to have cancer

## Faecal Immunochemical Test (FIT)

The NHS has a national screening programme offering screening every 2 years to all men and women aged 60 to 74 years in England, 50 to 74 years in Scotland. Patients aged over 74 years may request screening

- **eligible patients are sent Fecal Immunochemical Test (FIT) tests through the post**
- **a type of fecal occult blood (FOB) test which uses antibodies that specifically recognize human hemoglobin (Hb)**
- **used to detect, and can quantify, the amount of human blood in a single stool sample**
- **patients with abnormal results are offered a colonoscopy**

The **FIT test is also recommended for patients with new symptoms who do not meet the 2-week criteria** listed above, for example:

- patients >= 50 years with unexplained abdominal pain **OR** weight loss
- patients < 60 years with changes in their bowel habit **OR** iron deficiency anaemia
- patients >= 60 years who have anaemia even in the absence of iron deficiency

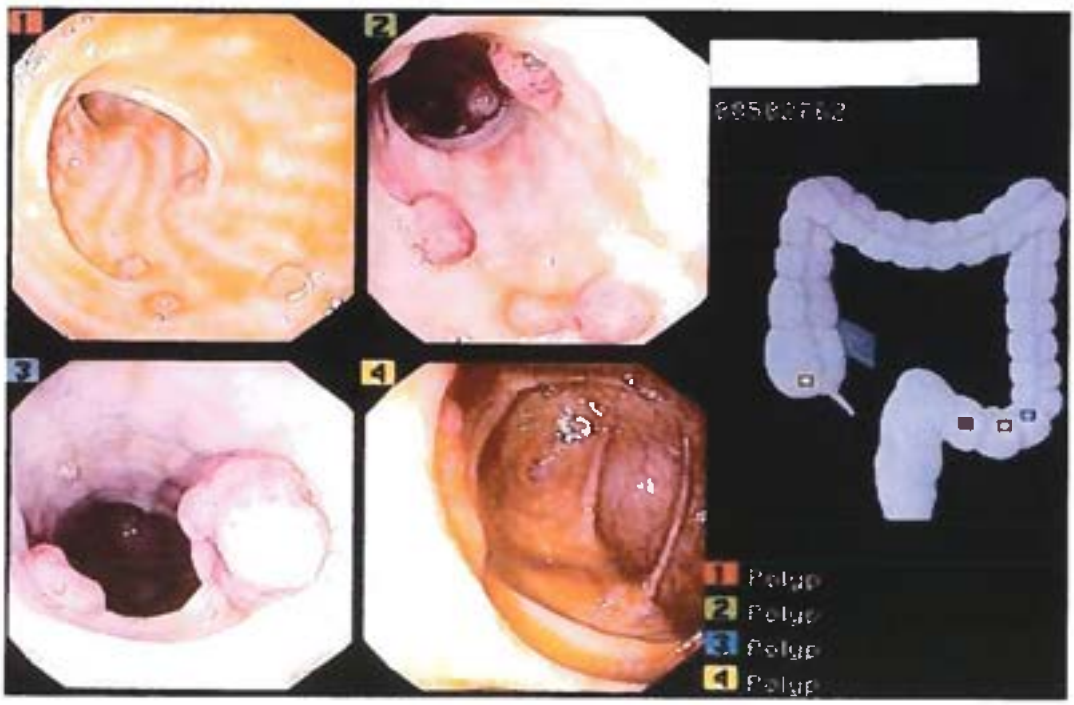
## Referral guidelines

NICE updated their referral guidelines in 2015. The following patients should be referred urgently (i.e. within 2 weeks) to colorectal services for investigation:

- patients >= 40 years with unexplained weight loss **AND** abdominal pain
- patients >= 50 years with unexplained rectal bleeding
- patients >= 60 years with iron deficiency anaemia **OR** change in bowel habit
- tests show occult blood in their faeces (see below)

**An urgent referral (within 2 weeks) should be 'considered' if:**

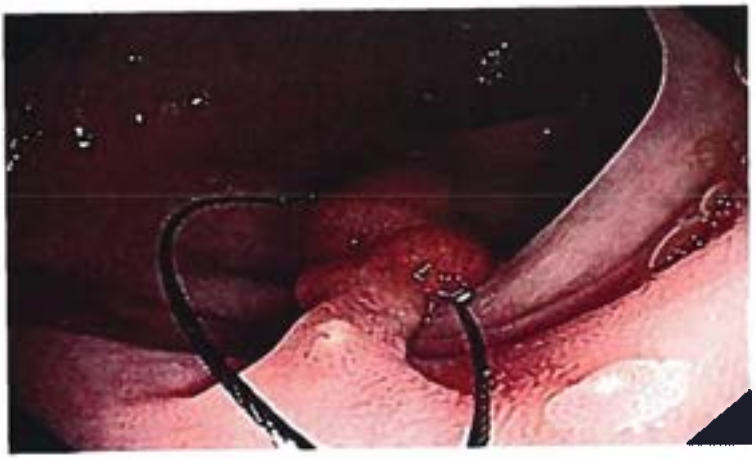
- there is a rectal or abdominal mass
- there is an unexplained anal mass or anal ulceration
- patients < 50 years with rectal bleeding **AND** any of the following unexplained symptoms/findings:
  - abdominal pain
  - change in bowel habit
  - weight loss
  - iron deficiency anaemia




Colon polyps seen on colonoscopy.

A 69-year-old woman with a family history of colon cancer presented for screening. Her hemoccult test was positive. Her double-contrast barium enema (air contrast) demonstrated a large colonic polyp, which was found on surgery to be highly dysplastic.

While getting a barium enema for other reasons, this patient was found to have a large colonic polyp. Biopsy of the polyp demonstrated early-stage colon cancer,



Polypectomy being performed through the colonoscope.

## Management

### Metastatic lesion resection:

- Colorectal carcinoma is one of the only oncological diseases where the presence of a metastatic deposit can be treated with curative intent.
- A solitary liver lesion should be surgically resected.
- Trans arterial chemoembolization & Radiofrequency ablation are used as palliative procedures when the lesions are too numerous or large to resect.

## Cowden's syndrome

- **Multiple hamartomatous polyps in GIT**
- With characteristic **mucocutaneous lesions** such as oral mucosal papillomas, palmoplanter keratosis, trichilemmomas (benign tumour of hair follicles).
- It is important to **diagnose early** because of the high risk of **malignancy**, particularly of breast and thyroid.
- **Thyroid dysfunction** is common even in the absence of cancer.

**Gardener's syndrome:**
It is a **rare** familial **autosomal dominant** condition characterized by **multiple small** and **large** intestinal **polyposis** tumours + **Osteomas** + **soft tissue tumours** (multiple lipomas, fibromas, and epidermoid cysts).
It carries an increased risk of **papillary carcinoma of the thyroid**.
**Colonic carcinoma** develops in 7% of individuals by age 21 years, 50% by age 39 years and 90% by age 45 years.
**Colectomy** is recommended once polyps appear.

## Hamartomatous polyposis syndrome

**Multiple hamartomatous polyps** in GIT by endoscopy suggest the presence of one of the **hamartomatous polyposis syndrome**:

- Familial juvenile polyposis.
- Cowden's syndrome: (see below)
- Peutz-Jeghers syndrome
- Neurofibromatosis type I
- MEN syndrome type II b

**These syndromes are** distinct from **the more common adenomatous syndromes** like

- HNPCC (Hereditary non-polyposis colon cancer) and
- FAP (Familial adenomatous polyposis).

## Meckel's diverticulum

Meckel's diverticulum is the vestigial remnant of the omphalomesenteric duct. It is normally located in **the terminal ileum within ~60 cm of the ileocaecal valve** and it averages **6 cm in length**.
About **50%** of these contain **ectopic gastric mucosa**, commonly leading to clinical presentations of peptic ulceration and haemorrhage.

### Pathophysiology

- normally, in the foetus, there is an attachment between the vitelliointestinal duct and the yolk sac. This disappears at 6 weeks gestation
- the tip is free in the majority of cases
- associated with enterocystomas, umbilical sinuses, and omphaloileal fistulas.
- arterial supply: omphalomesenteric artery.
- typically lined by ileal mucosa but ectopic gastric mucosa can occur, with the risk of peptic ulceration. Pancreatic and jejunal mucosa can also occur.

### Investigation

- if the child is haemodynamically stable with less severe or intermittent bleeding then a 'Meckel's scan' should be considered
  - uses 99m technetium pertechnetate, which has an affinity for gastric mucosa
- mesenteric arteriography may also be used in more severe cases e.g. transfusion is required

### Management

- removal if narrow neck or symptomatic
  - options are between wedge excision or formal small bowel resection and anastomosis

### Other complications of Meckel's diverticulum include

- Diverticulitis
- Intussusception
- Perforation
- Obstruction.

Although it occurs much more commonly in **children** it is an important differential consideration for gastrointestinal bleed in adults.
**Tc-99m pertechnetate** accumulates in gastric mucosa and is the study of choice for identifying ectopic gastric mucosa in a Meckel's diverticulum.

**EX**: A 14-year-old boy presents with a 2 day history of right lower quadrant abdominal pain and passage of bright red blood per rectum.
O/E there is tender in the right iliac fossa and bright red blood was found on rectal examination >>>? **Meckel's diverticulum** >>> pre-operatively diagnosis is by **Tc-99m pertechnetate.**

## Capsule endoscopy

- Capsule endoscopy is currently used in UK to identify the source of occult gastrointestinal bleeding when an OGD and colonoscopy and failed to show a cause.
- It is particularly useful for identifying pathology in the ileum.

## Clostridium difficile

Clostridium difficile is a **Gram-positive** rod often encountered in hospital practice. It produces an exotoxin which causes intestinal damage leading to a syndrome called pseudomembranous colitis.
Clostridium difficile develops when the normal gut flora is suppressed by broad-spectrum antibiotics.
**Clindamycin** is historically associated with causing Clostridium difficile but the aetiology has evolved significantly over the past 10 years.
**Second and third generation cephalosporins are now the leading cause of Clostridium difficile.**

### Other than antibiotics, risk factors include:

- **proton pump inhibitors**

## Features

- diarrhea
- abdominal pain
- a **raised white blood cell count (WCC)** is characteristic
- if severe toxic megacolon may develop

The Public Health England severity scale is often used as this may determine treatment:

| Mild | Moderate | Severe | Life-threatening |
|---|---|---|---|
| Normal WCC | ↑ WCC < 15 x $10^9$/L. Typically 3-5 loose stools per day | -↑ WCC > 15 x $10^9$/L<br>-or an acutely ↑ creatinine (> 50% above baseline)<br>-or a temperature > 38.5°C<br>-or evidence of severe colitis (abdominal or radiological signs) | -Hypotension<br>-Partial or complete ileus<br>-Toxic megacolon, or CT -evidence of severe disease |

## Diagnosis

- is made by detecting *Clostridium difficile* **toxin A and B** (CDT) **in the stool**
- *Clostridium difficile* **antigen** positivity only shows exposure to the bacteria, rather than current infection.

## Management

Current antibiotic therapy should be reviewed and antibiotics stopped if possible.

**Antibiotic treatment for Clostridium difficile (NICE guideline 2021)**

| Treatnment | Antibiotic |
|---|---|
| **First-line** for a first episode of mild, moderate or severe C. difficile infection | **Vancomycin:**125 mg orally four times a day for 10 days |
| Second-line for a first episode of mild, moderate or severe C. difficile infection if vancomycin is ineffective | **Fidaxomicin:** 200 mg orally twice a day for 10 days |
| **Third-line:** if first- and second-line are ineffective | **Vancomycin:** Up to 500 mg orally four times a day for 10 days With or **without Metronidazole** 500 mg intravenously three times a day for 10 days |
| **For relapse:** (a further episode of C. difficile infection within 12 weeks of Symptom resolution) | **Fidaxomicin:** 200 mg orally twice a day for 10 days |
| **For recurrence:** (a further episode of C. difficile infection **more than 12 weeks** after symptom resolution) | **Vancomycin:**125 mg orally four times a day for 10 days Or **Fidaxomicin:** 200 mg orally twice a day for 10 days |

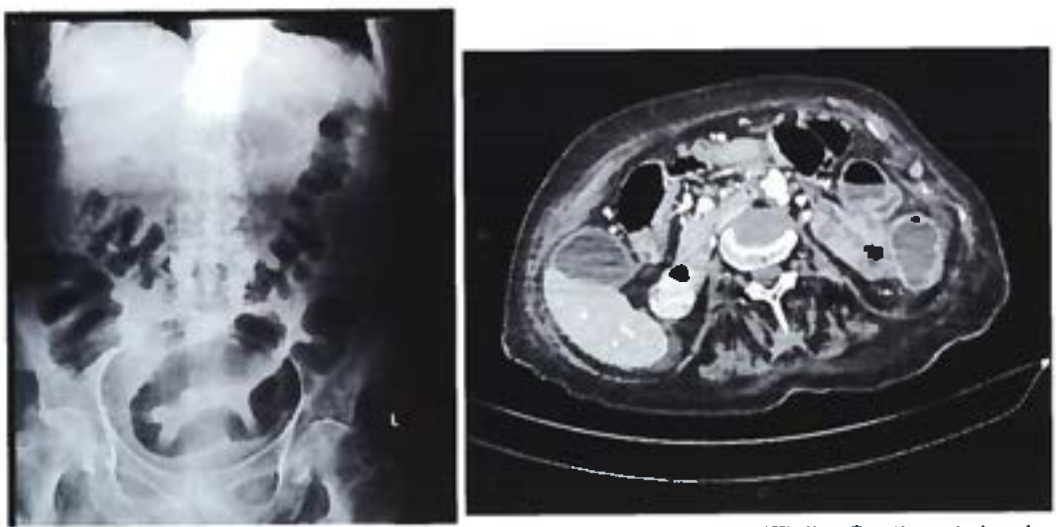
| | |
|---|---|
| **For life-threatening** C. difficile infection (Need urgent surgical assessment) | **Vancomycin:** 500 mg orally four times a day for 10 days **With Metronidazole:** 500 mg intravenously three times a day for 10 days |

## Recurrent episode

- recurrent infection occurs in around 20% of patients, increasing to 50% after their second episode
- **within 12 weeks of symptom resolution:** oral fidaxomicin
- **after 12 weeks of symptom resolution:** oral vancomycin OR fidaxomicin

## Other therapies

- **bezlotoxumab** is a monoclonal antibody which targets Clostridium difficile toxin B
  - NICE do not currently support its use to prevent recurrences as it is not cost-effective
- fecal microbiota transplant
  - may be considered for patients who've had 2 or more previous episodes.



Elderly lady with infectious colitis secondary to *Clostridium difficile*. On the abdominal film note the loss of bowel wall architecture and thumb-printing consistent with colitis. The CT from the same patient is enhanced by oral contrast. There is moderate free fluid in pelvis and peritoneum. The colon is oedematous throughout with enhancing walls, but of normal calibre. The sigmoid colon is smooth and featureless. Small bowel, liver, spleen, kidneys, adrenals and pancreas are normal.

**NB: Plain AXR** is useful for **diagnosing toxic dilatation** and would be the investigation of choice in patient with abdominal distension. Toxic dilatation should be excluded **prior** to sigmoidoscopy. However it does not establish the diagnosis.

**NB**: If **sigmoidoscopy** done>>>> will shows multiple white plaques adhered to the gastrointestinal mucosa.

The major pharmacologic advantage of oral vancomycin over metronidazole is that **oral vancomycin is not absorbed**, so **maximal concentrations** of the drug can act intracolonically at the site of infection.

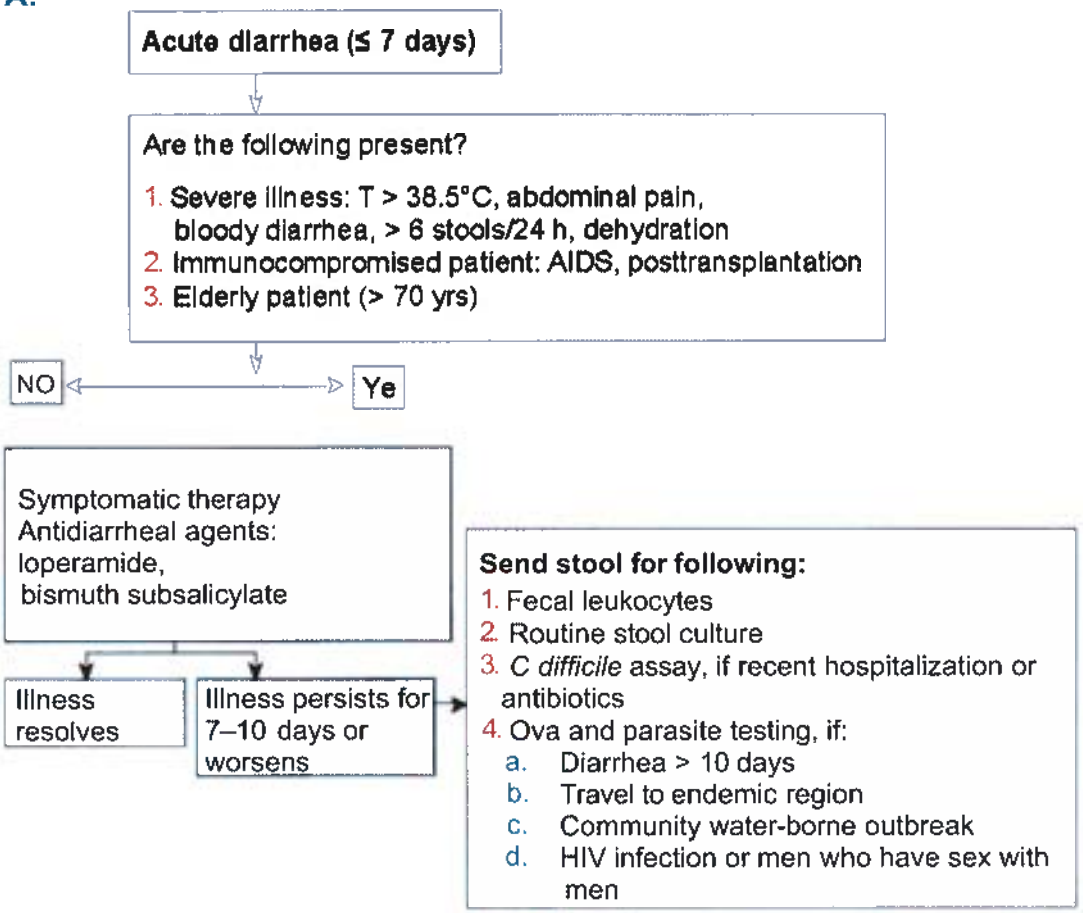
IV Metronidazole can be used where oral administration is impossible.

IV Vancomycin is not effective.

The instillation of **intracolonic vancomycin (as a retention enema)** is sometimes used as an adjunct to the treatment of severe disease.

## Diagrams for approaching cases of acute and chronic diarrhea

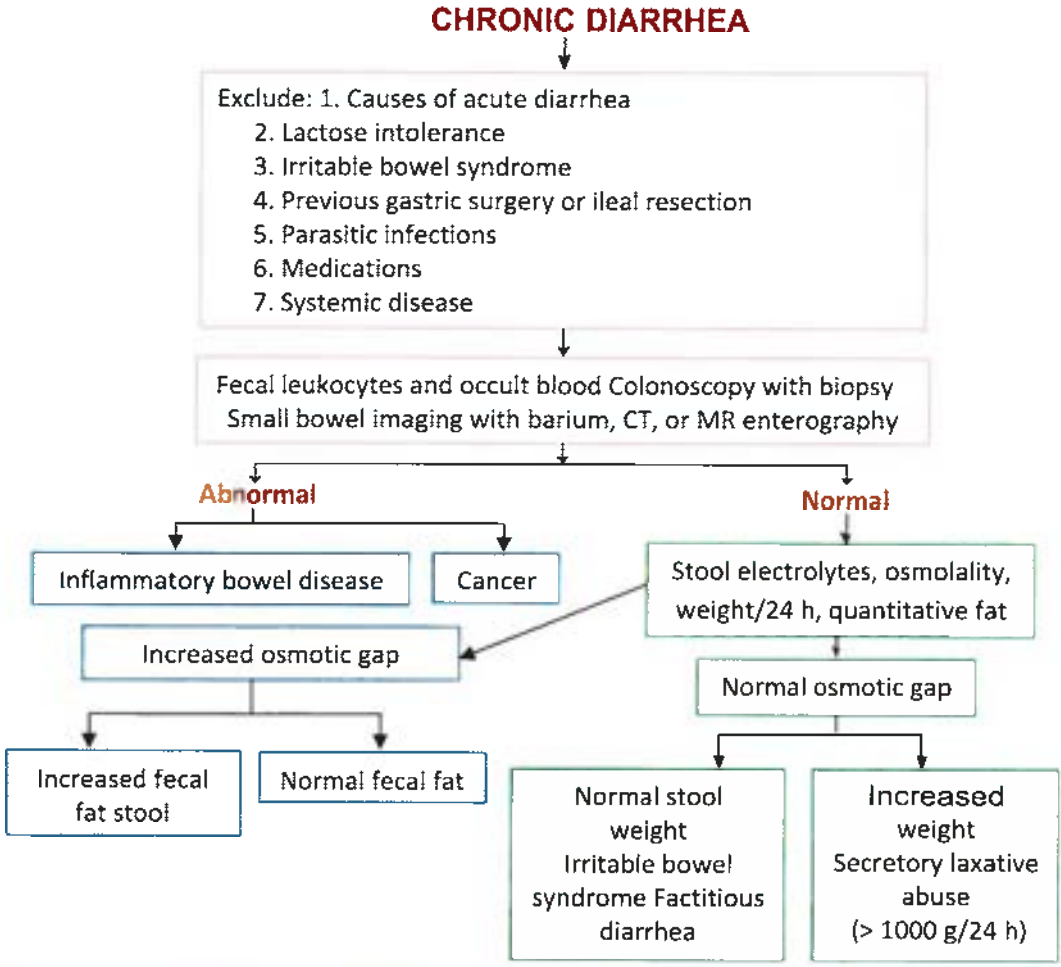
**A.**


Acute diarrhea (≤ 7 days)
Are the following present?
1. Severe illness: T > 38.5°C, abdominal pain, bloody diarrhea, > 6 stools/24 h, dehydration
2. Immunocompromised patient: AIDS, posttransplantation
3. Elderly patient (> 70 yrs)
NO
Ye
Symptomatic therapy
Antidiarrheal agents:
loperamide,
bismuth subsalicylate
Illness resolves
Illness persists for 7–10 days or worsens
Send stool for following:
1. Fecal leukocytes
2. Routine stool culture
3. C difficile assay, if recent hospitalization or antibiotics
4. Ova and parasite testing, if:
a. Diarrhea > 10 days
b. Travel to endemic region
c. Community water-borne outbreak
d. HIV infection or men who have sex with men

**Consider empiric antibiotic therapy while awaiting culture, if:**

1. Fecal leukocytes positive
2. Bloody diarrhea, fever, abdominal pain
3. Dehydration or > 8 stools/24 h
4. Immunocompromised
5. Hospitalization required

**B.**


CHRONIC DIARRHEA
Exclude: 1. Causes of acute diarrhea
2. Lactose intolerance
3. Irritable bowel syndrome
4. Previous gastric surgery or ileal resection
5. Parasitic infections
6. Medications
7. Systemic disease
Fecal leukocytes and occult blood Colonoscopy with biopsy
Small bowel imaging with barium, CT, or MR enterography
Abnormal
Normal
Inflammatory bowel disease
Cancer
Stool electrolytes, osmolality, weight/24 h, quantitative fat
Increased osmotic gap
Normal osmotic gap
Increased fecal fat stool
Normal fecal fat
Normal stool weight Irritable bowel syndrome Factitious diarrhea
Increased weight Secretory laxative abuse (> 1000 g/24 h)

## Gastroenteritis

- Gastroenteritis may either occur whilst at home or whilst travelling abroad (travellers' diarrhoea).
- Travellers' diarrhoea may be defined as at least 3 loose to watery stools in 24 hours with or without one of more of abdominal cramps, fever, nausea, vomiting or blood in the stool.
- The most common cause is **Escherichia coli.**
- Another pattern of illness is 'acute food poisoning'. This describes the sudden onset of nausea, vomiting and diarrhoea after the ingestion of a toxin.

- Acute food poisoning is typically caused by *Staphylococcus aureus*, *Bacillus cereus* or *Clostridium perfringen*.

| Infection | Typical presentation |
|---|---|
| **Escherichia coli** | **Common** amongst **travellers**<br>Watery stools<br>Abdominal cramps and nausea |
| **Giardiasis** | **Prolonged**, non-bloody diarrhoea |
| **Cholera** | Profuse, watery diarrhoea<br>Severe dehydration resulting in weight loss<br>Not common amongst travellers |
| **Shigella** | **Bloody** diarrhoea<br>Vomiting and abdominal pain |
| **Staphylococcus aureus** | Severe vomiting<br>Short incubation period |
| **Campylobacter** | A flu-like prodrome is usually followed by **crampy** abdominal pains frequently localising to the **right iliac fossa**, fever and **diarrhoea** which may be **bloody.**<br><br>Usually arise from eating **undercooked frozen food** e.g. **barbeques**.<br><br>Complications include **Guillain-Barre syndrome**, **Reactive arthritis** (Reiter's syndrome).<br><br>The symptoms are usually self-limiting, lasting up to 5 days.<br><br>**Treatment: Supportive** as fluid replacement and anti-emetics, antibiotics is controversial: erythromycin. |
| **Bacillus cereus** | **Two types of illness are seen**<br>• **Profuse vomiting** within **6 hours**, after eating **rice (Chinese restaurant).**<br>• Diarrhoeal illness occurring after 6 hours |
| **Amoebiasis** | **Gradual** onset **bloody** diarrhoea, abdominal pain and tenderness which may last for several weeks |
| **Norovirus** | **Rapid** presentation within 12 hours, **severe unremitting** vomiting, diarrhoea, associated with a number of virtually **simultaneous cases** like in the same class, often during the **winter** months e.g. November.<br>**Treatment:** supportive (ORT). |

## Incubation period:

- 1-6 hrs: Staphylococcus aureus, Bacillus cereus*
- 12-48 hrs: Salmonella, Escherichia coli
- 48-72 hrs: Shigella, Campylobacter
- > 7 days: **Giardiasis, Amoebiasis**

*Vomiting subtype, the diarrhoeal illness has an incubation period of 6-14 hours

**NB**: **E. coli** is the most common cause of travellers' diarrhoea and is usually a self-limiting condition, usually no treatment or investigation is required for this brief diarrhoeal illness.

**Cholera** and **giardiasis** are associated with **watery** diarrhoea.
**Giardia** is been reported as a cause of **chronic diarrhoea** with **weight loss**.
**Shigellosis** is a possible cause of **profuse bloody** diarrhoea.

**Trophozoites** and **cysts** are seen in **acute** amoebic dysentery, however cysts may also be excreted in asymptomatic carrier states.

**Bloody diarrhoea**: **Campylobacter,** then **Shigella** and **salmonella**.

**EX**: A group of workers presented to the ER with diarrhoea, flushing, sweating and a hot mouth. They fell ill **minutes** after eating lunch in the staff canteen. They had eaten **tuna fish**.

What is the likely cause of food poisoning?

**Scombroid poisoning** is associated with consumption of Scombridae, dark meat fish such as tuna, mackerel and marlin.

The most common cause of scombroid poisoning is due to ingestion of spoiled fish following inadequate refrigeration or prolonged time at room temperature. Cooking does not inactivate the toxin/histamines.

**Scombrotoxin food poisoning** is caused by the ingestion of foods that contain high levels of histamine and possibly other vasoactive amines and compounds. Histamine and other amines are formed by the growth of certain bacteria and the subsequent action of their decarboxylase enzymes on histidine and other amino acids in food, by spoilage of foods such as **fishery** products, particularly **tuna** or mahi mahi. Incubation period is **10-60 minutes**.

The definition of **chronic diarrhoea** is the abnormal passage of **3 or more** loose or liquid stools per day for **more than 4 weeks** and/or **a daily stool volume > 200 ml/day (weight > 200 g/day).**

### Traveller diarrhoea:

- It is usually caused by **enterotoxigenic E.coli** or **rota virus**.
- E. coli usually produce copious diarrhoea with minimal fever.
- It is not helpful to send stool culture.
- treatment:
  - Main treatment to **drink large amount of oral fluids**.
  - You should start **antibiotics if the condition persist for > 3 days.**
  - **Ciprofloxacin ± Loperamide**
  - **Osmotic diarrhoea** occurs in patients with diabetes who ingest too much sorbitol (a common substitute for glucose in so-called 'diabetic foods'.
  - **Secretory diarrhoea** commonly occurs in response to endotoxin-producing bacteria, (eg cholera or Escherichia coli).
  - **Chronic radiation enteritis** is diagnosed if diarrhoea and abdominal pain persist for 3 or more months following irradiation.

## Acute appendicitis

Acute appendicitis is the most common acute abdominal condition requiring surgery. It can occur at any age but is most common in young people aged 10-20 years.

### Pathogenesis

- lymphoid hyperplasia or a faecolith → obstruction of appendiceal lumen → gut organisms invading the appendix wall → oedema, ischaemia +/- perforation

### Abdominal pain is seen in the vast majority of patients:

- peri-umbilical abdominal pain (visceral stretching of appendix lumen and appendix is midgut structure) radiating to the right iliac fossa (RIF) due to localised parietal peritoneal inflammation.
- the migration of the pain from the centre to the RIF has been shown to be one of the strongest indicators of appendicitis
- patients often report the pain being worse on coughing or going over speed bumps. Children typically can't hop on the right leg due to the pain.

## Other features:

- vomit once or twice but marked and persistent vomiting is unusual
- diarrhoea is rare. However, pelvic appendicitis may cause localised rectal irritation of some loose stools. A pelvic abscess may also cause diarrhoea
- mild pyrexia is common - temperature is usually 37.5-38°C. Higher temperatures are more typical of conditions like mesenteric adenitis
- anorexia is very common. It is very unusual for patients with appendicitis to be hungry
- around 50% of patients have the typical symptoms of anorexia, peri-umbilical pain and nausea followed by more localised right lower quadrant pain

## Examination

- generalised peritonitis if perforation has occurred or localised peritonism
  - rebound and percussion tenderness, guarding and rigidity
- retrocaecal appendicitis may have relatively few signs
- digital rectal examination may reveal boggy sensation if pelvic abscess is present, or even right-sided tenderness with a pelvic appendix
- classical signs
  - Rovsing's sign (palpation in the LIF causes pain in the RIF) is now thought to be of limited value
  - psoas sign: pain on extending hip if retrocaecal appendix

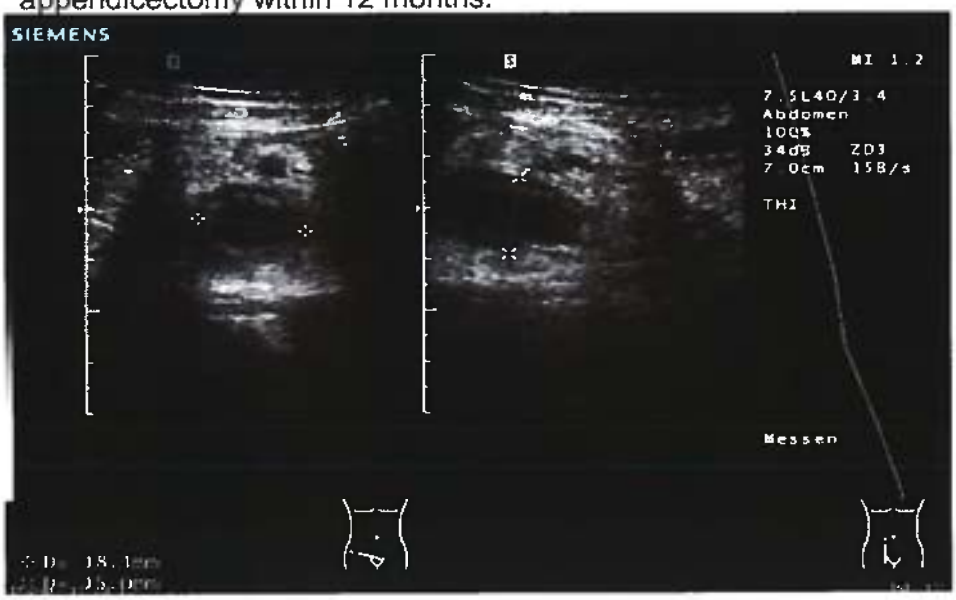
## Diagnosis

- typically raised inflammatory markers coupled with compatible history and examination findings should be enough to justify appendicectomy
- a neutrophil-predominant leucocytosis is seen in 80-90%
- urine analysis: useful to exclude pregnancy in women, renal colic and urinary tract infection. In patients with appendicitis, urinalysis may show mild leucocytosis but no nitrites
- there are no definite rules on the use of imaging and its use is often determined by the patient's gender, age, body habitus and the likelihood of appendicitis
  - thin, male patients with a high likelihood of appendicitis may be diagnosed clinically
  - ultrasound is useful in females where pelvic organ pathology is suspected. **Although it is not always possible to visualise the appendix on ultrasound,** the presence of free fluid (always pathological in males) should raise suspicion

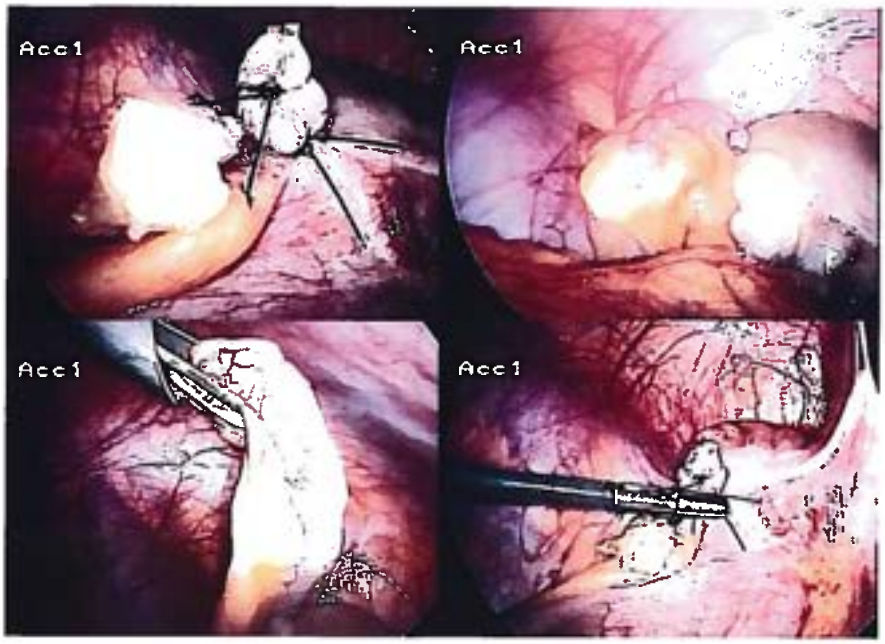
- CT scans are widely used in patients with suspected appendicitis in the US but this practice has not currently reached the UK, due to the concerns regarding excessive ionising radiation and resource limitations

## Management

- appendicectomy
  - can be performed via either an open or laparoscopic approach
  - laparoscopic appendicectomy is now the treatment of choice
- administration of **prophylactic intravenous antibiotics** reduces wound infection rates
- patients with perforated appendicitis (typical around 15-20%) require copious abdominal lavage.
- patients without peritonitis who have an appendix mass should receive broad-spectrum antibiotics and consideration given to performing an interval appendicectomy
- be wary in the older patients who may have either an underlying caecal malignancy or perforated sigmoid diverticular disease.
- trials have looked at the use of intravenous antibiotics alone in the treatment of appendicitis. The evidence currently suggests that whilst this is successful in the majority of patients, it is associated with a longer hospital stay and up to 20% of patients go on to have an appendicectomy within 12 months.




Ultrasound examination may show evidence of luminal obstruction and thickening of the appendiceal wall as shown below




Laparoscopic appendicectomy is becoming increasing popular as demonstrated below

## Gastrointestinal parasitic infections

**Common infections**

| Organism | Notes |
|---|---|
| **Enterobiasis** | • Due to organism *Enterobius vermicularis*<br>• Common cause of pruritus ani<br>• Diagnosis usually made by placing scotch tape at the anus, this will trap eggs that can then be viewed microscopically<br>• Treatment is with mebendazole |
| **Ancylostoma duodenale** | • Hookworms that anchor in proximal small bowel<br>• Most infections are asymptomatic although may cause iron deficiency anaemia<br>• Larvae may be found in stools left at ambient temperature, otherwise infection is difficult to diagnose<br>• Infection occurs as a result of cutaneous penetration, migrates to lungs, coughed up and then swallowed<br>• Treatment is with mebendazole |

| | |
|---|---|
| **Ascariasis** | • Due to infection with roundworm *Ascaris lumbricoides*<br>• Infections begin in gut following ingestion, then penetrate duodenal wall to migrate to lungs, coughed up and swallowed, cycle begins again<br>• Diagnosis is made by identification of worm or eggs within faeces<br>• Treatment is with mebendazole |
| **Strongyloidiasis** | • Due to infection with *Strongyloides stercoralis*<br>• Rare in west<br>• Organism is a nematode living in duodenum of host<br>• Initial infection is via skin penetration. They then migrate to lungs and are coughed up and swallowed. Then mature in small bowel are excreted and cycle begins again<br>• An auto infective cycle is also recognised where larvae will penetrate colonic wall<br>• Individuals may be asymptomatic, although they may also have respiratory disease and skin lesions<br>• Diagnosis is usually made by stool microscopy<br>• In the UK mebendazole is used for treatment |
| **Cryptosporidium** | • Protozoal infection<br>• Organisms produce cysts which are excreted and thereby cause new infections<br>• Symptoms consist of diarrhoea and cramping abdominal pains. Symptoms are worse in immunosuppressed people<br>• Cysts may be identified in stools<br>• Treatment is with metronidazole |

## Carcinoid syndrome

### Carcinoid tumours:

- It is a neuroendocrine tumour, which originate from **enterochromaffin** cells of the **intestine**.
- Usually occurs when **metastases** are present in the **liver** and release **serotonin (5-HT)** into the **systemic** circulation which will cause **flushing**, **diarrhoea** and **bronchospasm**.
- They are indolent tumours secreting more than 20 different hormones, likely 5-HT, kinins, prostaglandins and other vasoactive substances are secreted.

- Most of cases with more than **95%** of patients with carcinoid tumour have **liver metastasis** at the time of diagnosis.
- The carcinoid syndrome **only** arises **when liver metastases are present** and the tumour products being metabolised by the liver by draining directly into the hepatic veins.
- May also occur with lung carcinoid as mediators are not 'cleared' by the liver.
- The most common sites for the primary tumour are the **appendix (40%), terminal ileum (30%), rectum (20%),** and less commonly in the bronchus, ovary and testis.
- 80% of tumours greater than 2 cm in diameter will metastasize.
- **Very bad prognosis**: **average survival** is **5-10 years from diagnosis**

## Features:

- **Flushing** (often **earliest** symptom) in **75-90%** of cases, it is caused due to release of vasoactive compounds such as 5-HT and bradykinin, it is often provoked by alcohol.
- **Hypotension**
- Chronic **diarrhoea** (in > **70%**).
- **Bronchospasm** (in **25%**).
- **Right heart valvular stenosis e.g. tricuspid regurgitation / pulmonary stenosis** is found in **50%** of cases and can lead to right-sided CHF like LL oedema (left heart can be affected in bronchial carcinoid).
- **Pellagra** can rarely develop as dietary tryptophan is diverted to serotonin by the tumour.
- Other molecules such as ACTH and GHRH may also be secreted resulting in, for example, Cushing's syndrome.

The **triad** of **facial flushing**, **chronic diarrhoea** and **cardiac** involvement represents more than **85%** of symptoms of carcinoid syndrome.

## Investigations:

- **High 24-hour urinary 5-HIAA excretion:** (5-hydroxyindoleacetic acid) - is greater than 0.3 mmol.
- **Abdominal US:**to visualise the liver metastasis.
- **Chest and abdomen CT**
- Plasma chromogranin A y

## Management: (mainly palliative):

- Somatostatin analogues e.g., **Octreotide.**
- **Symptomatic** control, as diarrhoea: cyproheptadine may help

- Surgery to debulk the tumour
- Trans-arterial embolisation and radioisotope therapy.
- Telostristat approved by (FDA) in 2017 for carcinoid syndrome diarrhea in combination with somatostatin analog (SSA) therapy in adults inadequately controlled by an SSA.

**EX:** A 65-year-old man known to have a carcinoid tumour of the appendix is found to have hepatic metastases. If the patient develops carcinoid syndrome, what is the first symptom most likely to occur? >>> **Flushing.**

**NB:** The worst prognostic feature in carcinoid syndrome is **valvular** heart disease. Cardiac lesions are not reversible with treatment, deteriorate with time and frequently require replacement. Most patients die of progressive right heart failure within one year after onset of symptoms.

## Pseudomyxoma peritonei

- Pseudomyxoma peritonei is a rare mucinous tumour most commonly arising from the appendix.
- The disease is characterised by the accumulation of large amounts of mucinous material in the abdominal cavity.
- It is rare, with an incidence of 1-2/1,000,000 per year

### Treatment

- usually surgical and consists of cytoreductive surgery (and often peritonectomy) combined with intra-peritoneal chemotherapy with mitomycin C.

# Pancreatic

## Acute pancreatitis

Acute pancreatitis is usually due to alcohol or gallstones.

### Features:

- severe epigastric pain that may radiate through to the back
- vomiting is common
- examination may reveal epigastric tenderness, ileus and low-grade fever
- periumbilical discolouration (Cullen's sign) and flank discolouration (Grey-Turner's sign) is described but rare

**Rare features associated with pancreatitis include:**

- ischaemic (Purtscher) retinopathy - may cause temporary or permanent blindness

### Causes

**Popular mnemonic is GET SMASHED:**

- **G**allstones
- **E**thanol
- **T**rauma
- **S**teroids
- **M**umps (other viruses include Coxsackie B)
- **A**utoimmune (e.g. polyarteritis nodosa), **A**scaris infection
- **S**corpion venom
- **H**ypertriglyceridaemia, **H**yperchylomicronaemia, **H**ypercalcaemia, **H**ypothermia
- ERCP
- **D**rugs (**A**zathioprine, **M**esalazine, **S**ulphasalazine, 5 ASA, Didanosine, **B**endroflumethiazide, **F**urosemide, **G**LP-1 agonists, Pentamidine, Steroids, Oestrogen, Octreotide, **S**odium valproate, and **m**ethyldopa).
- **Post-burn pancreatitis**.

## Investigations:

### serum amylase

- raised in 75% of patients - typically > 3 times the upper limit of normal
- levels do not correlate with disease severity
- specificity for pancreatitis is around 90%. Other causes of raised amylase include: pancreatic pseudocyst, mesenteric infarct, perforated viscus, acute cholecystitis, diabetic ketoacidosis

### serum lipase

- more sensitive and specific than serum amylase
- it also has a longer half-life than amylase and may be useful for late presentations > 24 hours

### imaging

- a diagnosis of acute pancreatits can be made without imaging if characteristic pain + amylase/lipase > 3 times normal level
- however, early ultrasound imaging is important to assess the aetiology as this may affect management - e.g. patients with gallstones/biliary obstruction
- other options include contrast-enhanced CT

**N.B:**

- Pancreatitis is 7 times more common in patients taking mesalamines than sulfasalazine.
- Sodium valproate induced pancreatitis is more common in young adults and tends to occur within the first few months of treatment. Asymptomatic elevation of the amylase level is seen in up to 10% of patients.
- **CRP** is now a widely used marker of **severity** in acute pancreatitis. Other methods which have to correlate with prognosis include the **Ranson** criteria and **APACHE II** score (Acute Physiology and Chronic Health Evaluation).
- **Post-ERCP pancreatitis** (The acute pancreatitis following ERCP) should be treated with **IV fluids and analgesia**. **Quinolones** have **not** been shown to be beneficial in acute pancreatitis.
- Pancreatitis occurs in around **1 in 2,000 pregnancies**. Most cases of pancreatitis in pregnancy are **gallstone** related.
- **Hyperchylomicronaemia** may be caused by hereditary lipoprotein lipase **(LPL)** deficiency and apolipoprotein CII **(Apo CII)** deficiency. It predisposes to recurrent attacks of acute pancreatitis.
- The **mortality** associated with severe acute pancreatitis is approximately **20%**.

There are a number of criteria used in the **Ranson's scoring system** which reflect **prognosis** associated with **acute pancreatitis**.

CT from a patient with acute pancreatitis. Note the diffuse parenchymal enlargement with oedema and indistinct margins.

If ≥ **3** of these criteria within the 1st 48 hours >> **severe** pancreatitis >> **ICU**.

## Treatment:

of acute pancreatitis: **Oxygen therapy** and **fluid resuscitation** have been shown in RCT to reduce the chances of prolonged organ failure and so decrease the mortality. The use of antibiotics is debatable.

- supportive, and monitoring (often in the intensive care unit).
- Fluid resuscitation: aggressive hydration with crystalloids (e.g., normal saline)
- Analgesia: IV opioids (e.g., fentanyl)
- Bowel rest (NPO)and IV fluids are recommended until the pain subsides
- Nasogastric tube insertion:
  - not routinely recommended;
  - indicated in patients with vomiting and/or significant abdominal distention
- Nutrition
  - Begin **enteral feeding** (oral/nasogastric/naso-jejunal) **as soon as the pain subsides**
  - Total parenteral nutrition:
    - **only in patients who cannot tolerate enteral feeds** (e.g., those with persistent ileus and abdominal pain)
- if there is **gallstones**:
- urgent **ERCP** when stable.
- **All should have a cholecystectomy** either **during the same admission** or within four weeks depending on their clinical progress.

## Complications:

### Local complications

#### Peripancreatic fluid collections

- Occur in 25% cases
- Located in or near the pancreas and lack a wall of granulation or fibrous tissue
- May resolve or develop into pseudocysts or abscesses
- Since most resolve aspiration and drainage is best avoided as it may precipitate infection

#### Pancreatic pseudocyst:

- In acute pancreatitis result from organization of peripancreatic fluid collection. They may or may not communicate with the ductal system.
- The collection is walled by fibrous or granulation tissue and typically occurs 4 weeks or more after an attack of acute pancreatitis
- Most are retro gastric
- 75% are associated with persistent mild elevation of amylase
- Investigation is with CT, ERCP and MRI or endoscopic USS
- Symptomatic cases may be observed for 12 weeks as up to 50% resolve
- Treatment is either with endoscopic or surgical cystogastrostomy or aspiration

#### Pancreatic necrosis

- Pancreatic necrosis may involve both the pancreatic parenchyma and surrounding fat
- Complications are directly linked to extent of parenchymal necrosis and extent of necrosis overall
- Early necrosectomy is associated with a high mortality rate (and should be avoided unless compelling indications for surgery exist)
- Sterile necrosis should be managed conservatively (at least initially)
- Some centres will perform fine-needle aspiration sampling of necrotic tissue if infection is suspected. False negatives may occur and the extent of sepsis and organ dysfunction may be a better guide to surgery

#### Pancreatic abscess

- Intraabdominal collection of pus associated with pancreas but in the absence of necrosis
- Typically occur as a result of infected pseudocyst
- Transgastric drainage is one method of treatment, endoscopic drainage is an alternative

### Haemorrhage

- Infected necrosis may involve vascular structures with resultant haemorrhage that may occur de novo or as a result of surgical necrosectomy.
- When retroperitoneal haemorrhage occurs Grey Turner's sign may be identified

### Systemic complications

#### Acute respiratory distress syndrome

- associated with a high-mortality rate of around 20%
- WBC count 12,000/mm$^3$, less than 4000/mm$^3$ , or more than 10% immature (bands) form.

## Chronic pancreatitis

Chronic pancreatitis is an inflammatory condition which can ultimately affect **both** the **exocrine** and **endocrine** functions of the pancreas.

Approximately 60% of patients survive 2 years.

### Causes:

- **Alcohol**.
- **Cystic fibrosis**.
- Haemochromatosis.
- ductal obstruction: tumours, stones, structural abnormalities including pancreas divisum and annular pancreas
- Unknown.

Around **80%** of cases are due to **alcohol** excess with up to 20% of cases being unexplained.
The most common cause in **adult** is **alcohol**, and in **children** is **Cystic fibrosis**.

### Features:

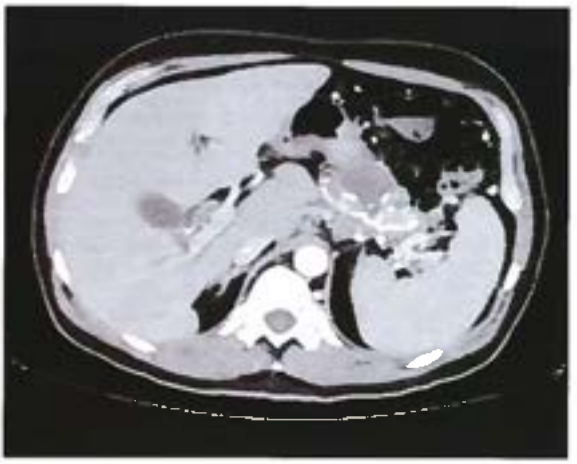
- **Pain** is typically worse 15 to 30 minutes following a meal
- **Steatorrhoea**: symptoms of pancreatic insufficiency usually develop between 5 and 25 years after the onset of pain
- **Diabetes mellitus** develops in the majority of patients. It typically occurs more than 20 years after symptom begin

### Investigation:

- Abdominal x-ray shows pancreatic calcification in 30% of cases
- **CT is more sensitive at detecting pancreatic calcification.**
- Sensitivity is 80%, specificity is 85%.

- **Functional tests:**
  - **Faecal elastase** may be used to assess exocrine function if imaging inconclusive.
  - **Secretin stimulation test.**
- **MRCP/ERCP** to rule out mass lesion if with significant weight loss.

x- ray abdomen showing multiple small calcific foci projected in the pancreas consistent with chronic pancreatitis.



CT showing an irregular shaped pancreas with the typical calcification of chronic pancreatitis

**Faecal elastase** is for test the **exocrine** pancreatic insufficiency.
It is non-invasive and can be performed **on a single stool sample**.
**Low** levels of faecal elastase are **indicative** of pancreatic exocrine deficiency and predictive of the response to supplementation.
(N= more than 200 Mcg/ gm faeces).

Even the **secretin stimulation test**, which is the **most sensitive** method of assessing pancreatic exocrine function, it is **invasive** and therefore not a preferred investigation. Also, it is probably abnormal only when more than 60% of exocrine function has been lost.

**Secretin stimulation test:**
It involves positioning a tube inside the duodenum and collecting pancreatic secretions stimulated by IV secretin alone or with either cholecystokinin.

Duodenal contents are collected for volume determination, HCO3 concentration and enzyme concentration.

**Normal volume is > 2 ml/kg** and **Normal HCO3 is > 80 mEq/l**

If **normal** volume (> 2ml/kg) + **low** HCO3 (< 80 mEq/l) >>> suggests **chronic pancreatitis.**

If **low** volume (< 2ml/kg) + **normal** HCO3 (> 80 mEq/l) + normal enzyme levels >>> **pancreatic duct obstruction** perhaps secondary to tumour and should prompt **ERCP**.

**Chronic pancreatitis** >>>> with **LOW HCO3**
**Pancreatic duct obstruction** >>>> with LOW **VOLUME**

**NB: Faecal fat excretion** is **high (> 30 gm/3 days)** (**steatorrhoea**) indicating pancreatic enzyme insufficiency almost obsolete .

## Management:

- Stop alcohol
- **Pancreatic enzyme supplements**
- Analgesia
- Antioxidants: limited evidence base - one study suggests benefit in early disease.

## Complications

- **Pancreatic pseudocysts**
- **Splenic vein thrombosis**
  - Occur in **10%** of patients with chronic pancreatitis
  - Pathophysiology: inflammation of the splenic vein → thrombus formation → left-sided portal hypertension → **gastric varices**
  - Clinical features: can present with upper GI bleeding, ascites, and splenomegaly

# Pancreatic cancer

## Features:

- Classically **painless obstructive jaundice.**
- However, patients typically present in a **non-specific way** with anorexia, nausea, malaise, mild epigastric pain, **recent onset DM and significant weight loss which is a characteristic feature.**
- Pancreatic cancer is the **3rd** most common malignancy affecting the GIT, but it is a **difficult disease to diagnose in its early stages** and therefore most patients present at an advanced and incurable stage.
- The most useful tumour marker for pancreatic cancer is **CA 19-9**, of which the sensitivity and specificity for pancreatic carcinoma are 80% and 90% respectively.
- CA 19-9 does not distinguish between cholangiocarcinoma, pancreatic or gastric carcinoma and may also be raised in patients with severe liver injury due to any other cause.
- The accuracy of using CA 19-9 to identify patients with small surgically resectable tumours is limited.

The history of **post-prandial abdominal pain** accompanied with **weight loss** and **intermittent diarrhoea** is consistent with **pancreatic involvement** >>>? **Pancreatic adenocarcinoma**

## Associations:

- **Smoking**
- **Diabetes**
- **Chronic pancreatitis**
- Hereditary pancreatitis
- Hereditary non-polyposis colorectal carcinoma
- Multiple endocrine neoplasia (MEN)
- Peutz-Jeghers syndrome (PJS)
- **BRCA2 gene**
- Dysplastic naevus syndrome
- increasing age
- KRAS gene mutation

## Investigation

- ultrasound has a sensitivity of around 60-90%
- **high resolution CT scanning is the investigation of choice** if the diagnosis is suspected

- Carbohydrate Antigen 19-9 (CA-19-9) is a tumour marker is usually used to monitor response to treatment and possible recurrance, rather than for diagnosis.

## Management:

- less than 20% are suitable for surgery at diagnosis
- a Whipple's resection (pancreaticoduodenectomy) is performed for resectable lesions in the head of pancreas.
  - Side-effects of a Whipple's include dumping syndrome and peptic ulcer disease
- adjuvant chemotherapy is usually given following surgery
- ERCP with stenting is often used for palliation

ERCP showing invasive ductal adenocarcinoma. Note the dilation of the common bile duct due to the pancreatic lesion

# Liver

## Liver function test

### Gamma-glutamyl-transferase (GGT)

- ↑↑ by drugs such as phenytoin and alcohol.
- Mild raises in GGT can occur with any alcohol intake, and a rise does not always indicate liver pathology.
- **↑↑ in fatty liver**

### Transaminase

- differential diagnosis for elevated serum aminotransferases:
  - viral hepatitis
  - hepatotoxicity from drugs or toxins
  - alcoholic liver disease
  - hepatic ischemia, and malignant infiltration
- **Only ischaemic hepatitis and paracetamol overdose tend to produce transaminase levels that are raised to very high degree (more than 100 times the upper limit of normal).**
- hypotension (particularly in an individual who is normally hypertensive) is the usual precipitant for ischaemic hepatitis.
- Remember that the level to which transaminases are elevated cannot be used to judge the degree of liver damage and impairment of hepatic function.
- Patients with a hepatocellular process generally have a disproportionate elevation in the serum aminotransferases compared with the alkaline phosphatase, while those with a cholestatic process have the opposite findings.
- AST/ALT ratio:
- fatty liver: AST/ALT usually <1
- alcohol abuse: AST/ALT ratio > 2:1

# Alkaline phosphatase

## Causes of raised alkaline phosphatase (ALP):

- Liver: cholestasis, hepatitis, fatty liver, neoplasia
  - In cholestasis, ALP is typicaly elevated to at least four times the upper limit of normal.
    - Lesser degrees of elevation are nonspecific and may be seen in other liver diseases
- Paget's
- Osteomalacia
- Bone metastases
- Hyperparathyroidism
- Renal failure
- Physiological: **pregnancy**, growing children, healing fractures

The table below splits the causes according to the calcium level:

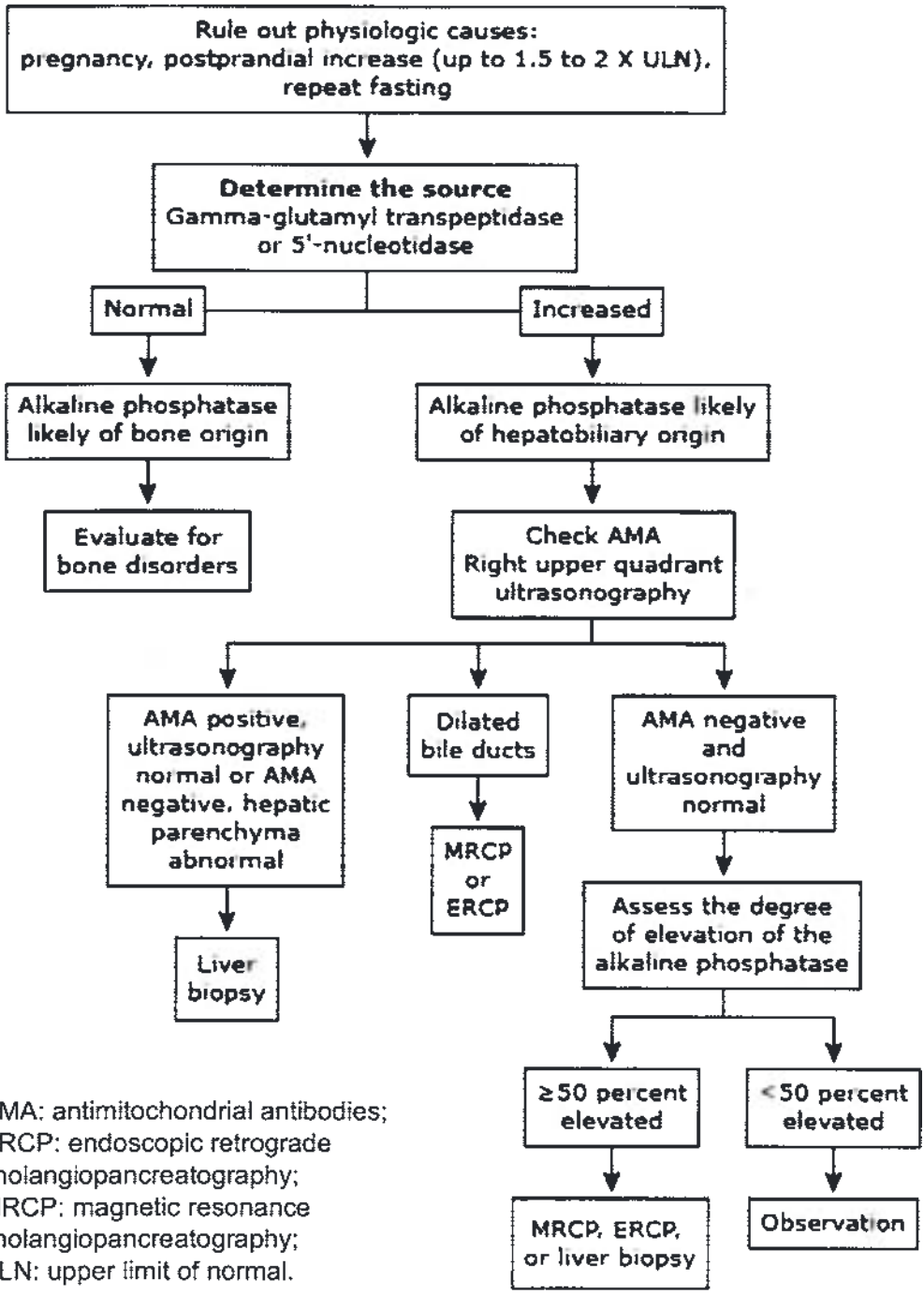
| Raised ALP and raised calcium | Raised ALP and low calcium |
|---|---|
| • Bone metastases<br>• Hyperparathyroidism | • Osteomalacia<br>• Renal failure |

**NB**: Alkaline phosphatase is significantly elevated in pregnancy.

If ALT is > 300 U/L you may suspect drug-induced, viral hepatitis, autoimmune hepatitis and ischaemic hepatitis.

**Raised IgA** can also be present in chronic active hepatitis and IgA nephropathy.
**Deficiency of IgA** produces autoimmune disorders, chronic diarrhoea and respiratory infections.
**Raised IgM** may be seen in primary biliary cirrhosis, Waldenström's macroglobulinaemia, infections .
**Reduced IgM** may be acquired or congenital and can be associated with myeloma.
**Raised IgE** in asthma, allergic Broncho pulmonary aspergillosis (ABPA), atopic dermatitis, psoriasis and parasitic diseases.

**Evaluation of elevated serum alkaline phosphatase (UpToDate)**


Rule out physiologic causes:
pregnancy, postprandial increase (up to 1.5 to 2 X ULN),
repeat fasting
Determine the source
Gamma-glutamyl transpeptidase
or 5'-nucleotidase
Normal
Increased
Alkaline phosphatase likely of bone origin
Alkaline phosphatase likely of hepatobiliary origin
Evaluate for bone disorders
Check AMA
Right upper quadrant ultrasonography
AMA positive, ultrasonography normal or AMA negative, hepatic parenchyma abnormal
Dilated bile ducts
AMA negative and ultrasonography normal
Liver biopsy
MRCP or ERCP
Assess the degree of elevation of the alkaline phosphatase
≥50 percent elevated
<50 percent elevated
MRCP, ERCP, or liver biopsy
Observation

AMA: antimitochondrial antibodies;
ERCP: endoscopic retrograde cholangiopancreatography;
MRCP: magnetic resonance cholangiopancreatography;
ULN: upper limit of normal.

# Hepatobiliary disease and related disorders

The table below gives characteristic exam question features for conditions causing hepatobiliary disease and related disorders:

| Condition | Features |
|---|---|
| **Viral hepatitis** | Common symptoms include:<br>• nausea and vomiting, anorexia<br>• myalgia<br>• lethargy<br>• right upper quadrant (RUQ) pain<br>Questions may point to risk factors such as foreign travel or intravenous drug use. |
| **Congestive hepatomegaly** | The liver only usually causes pain if stretched. One common way this can occur is as a consequence of congestive heart failure. In severe cases cirrhosis may occur. |
| **Biliary colic** | RUQ pain, intermittent, usually begins abruptly and subsides gradually. Attacks often occur after eating. Nausea is common.<br>It is sometimes taught that patients are female, forties, fat and fair although this is obviously a generalisation. |
| **Acute cholecystitis** | Pain similar to biliary colic but more severe and persistent. The pain may radiate to the back or right shoulder.<br>The patient may be pyrexial and Murphy's sign positive (arrest of inspiration on palpation of the RUQ) |
| **Ascending cholangitis** | An infection of the bile ducts commonly secondary to gallstones. Classically presents with a triad of:<br>• fever (rigors are common)<br>• RUQ pain<br>• jaundice |
| **Gallstone ileus** | This describes small bowel obstruction secondary to an impacted gallstone. It may develop if a fistula forms between a gangrenous gallbladder and the duodenum.<br>Abdominal pain, distension and vomiting are seen. |
| **Cholangiocarcinoma** | Persistent biliary colic symptoms, associated with anorexia, jaundice and weight loss. A palpable mass in the right upper quadrant (Courvoisier sign), periumbilical lymphadenopathy (Sister Mary Joseph nodes) and left supraclavicular adenopathy (Virchow node) may be seen |

| Condition | Features |
|---|---|
| **Acute pancreatitis** | Usually due to alcohol or gallstones<br>Severe epigastric pain<br>Vomiting is common<br>Examination may reveal tenderness, ileus and low-grade fever<br>Periumbilical discolouration (Cullen's sign) and flank discolouration (Grey-Turner's sign) is described but rare |
| **Pancreatic cancer** | Painless jaundice is the classical presentation of pancreatic cancer. However pain is actually a relatively common presenting symptom of pancreatic cancer. Anorexia and weight loss are common |
| **Amoebic liver abscess** | Typical symptoms are malaise, anorexia and weight loss. The associated RUQ pain tends to be mild and jaundice is uncommon. |

# Hepatitis B

Hepatitis B is a double-stranded DNA virus and is spread through exposure to infected blood or body fluids, including **vertical transmission** from mother to child. The incubation period is **6-20 weeks.**

**Perinatal transmission** is the **most common route** of HBV infection - the infection rate is **90%** in infants born to **HBeAg positive mothers.**

Blood inoculation through unclean needles is **not** the commonest route of transmission of hepatitis B but this remains important.
Sexual transmission comprises 30% of HBV infections in developed countries.

## Hepatitis B serology:

| Marker | HBeAg-positive infection | HBeAg-positive hepatitis | HBeAg-negative infection | HBeAg-negative hepatitis | Resolved infection |
|---|---|---|---|---|---|
| HBsAg | High | Intermediate | Low | Intermediate | Negative |
| HBeAg | Positive | Positive | Negative | Negative | Negative |
| HBV DNA | Very high | High | <2000-20 000 IU/mL | >2000-20 000 IU/mL | Undetectable |
| ALT | Normal | Increased | Normal | Increased | Normal |
| Risk for disease progression | Minimal | Yes | Minimal | Yes | None |
| Treatment | Monitor | NA/PEG-IFN | Monitor | NA/PEG-IFN | None* |
| LHBs | | | Low | High | |
| Anti-HBc | Low | High | Low | High | Positive |
| HBcrAg | Very high | High | Intermediate | Low | Undetectable |
| HBV RNA | Very high | High | High-intermediate | Intermediate-low | |

ALT, alaninaminotransferase; IU, international units; NA, nucleos(t)ide analogues; PEG-IFN, pegylated interferon alfa; HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen; LHBs, large hepatitis B surface protein; anti-HBc, antibodies to hepatitis B core antigen; HBcrAg, hepatitis B core-related antigen; RNA, ribonucleic acid; DNA, deoxyribonucleic acid

The risk for disease progression and the need for treatment is indicated by colour shading: red: high risk for disease progression / treatment required, yellow: low risk for disease progression / monitoring required, green: no disease progression / no action required

*Monitor in case of cirrhosis or immunosuppression.

Interpreting hepatitis B serology is a dying art form which still occurs at regular intervals in medical exams. It is important to remember a few key facts:

- HBsAg is the first marker to appear and causes the production of HBsAb.
- The presence of HBsAg in the serum is indicative of **active HBV** infection, **either** acute or chronic.
- HBsAg normally implies **acute disease (present for 1-6 months).**

- If HBsAg if present **for > 6 months then this implies chronic disease (i.e. Infective) (i.e. a carrier).**
- HBsAb implies **immunity** (either exposure or immunisation).
- It is **negative in chronic disease.**
- Anti-HBc implies **previous (or current) infection.** IgM anti-HBc appears during acute or recent hepatitis B infection and is present for about 6 months. IgG anti-HBc can persist life long.
- HBcAb IgG is produced from around 14 weeks after exposure, in the absence of HBcAb IgM it may indicate **cleared or chronic HBV** infection.
- **HBeAg** results from breakdown of core antigen from infected liver cells as is therefore a marker of **infectivity** and **replication.**
- HBeAg negativity implies that the patient no longer has active infection.
- HBeAg is present in acute infection and may persist in chronic for several years.
- The phenomenon of loss of HBeAg and seroconversion to HBeAb positive status indicates a reduction of inflammation accompanied by histological change from active to inactive hepatitis.
- **HBeAg is a marker of infectivity** in **all** patients **except those** who have **HBV with pre-core mutant**, because they don't synthesize HBeAg, this is most commonly due to stop-codon mutation at nucleotide 1896. So the learning point here is that **although HBeAg is negative some patients still may have active HBV and is still infective.**

So not all negative HBeAg are not infective, may be **HBV with pre-core mutant** (negative HBeAg but still infective).

**Active** HBV infection means **any detectable DNA** in blood >>> needs treatment.

## Common example results:

- **Previous immunisation**: anti-HBs positive, all others negative.
- **Previous hepatitis B (> 6 months ago), not a carrier (= cleared):** anti-HBc IgG positive, HBsAg **negative.**
- **Previous hepatitis B, now a carrier (= chronic hepatitis):** anti-HBc IgG positive, HBsAg **positive.**

**NB**: The presence of **isolated HBcAb** signifies one of 3 possibilities:

1) The patient is in the period of acute hepatitis B between the disappearance of the HBsAg and the appearance of HBsAb.

2) HBsAb has fallen to undetectable levels following recovery from acute hepatitis B.
3) Chronic HBV infection where the HBsAg titre has fallen to undetectable levels.

**NB**: Patients who are **positive for HBsAg for more than 6 months** but are **HBe Ag negative**, **HBV DNA negative** and **have normal ALT** >>> do **not** require liver biopsy **nor** do they require antiviral therapy, only hepatitis B serology and ALT should be **monitored** annually.

| | HBsAg | Anti-HBs | Anti-HBc |
|---|---|---|---|
| Susceptible | - | - | - |
| Vaccinated | - | + | - |
| Past Infection | - | + | + |
| Acute Infection | + | - | + (IgM) |
| Chronic Infection | + | - | + (IgG) |

## Immunisation against hepatitis B:

- Contains HBsAg adsorbed onto aluminium hydroxide adjuvant and is prepared from yeast cells using **recombinant DNA technology**.
- Most schedules give 3 doses of the vaccine with a recommendation for a one-off booster 5 years following the initial primary vaccination.
- At risk groups who should be vaccinated include: healthcare workers, IV drug users, sex workers, and close family contacts of an individual with hepatitis B, individuals receiving blood transfusions regularly, chronic kidney disease patients who may soon require renal replacement therapy, prisoners, and chronic liver disease patients.
- Around 10-15% of adults fail to respond or respond poorly to 3 doses of the vaccine. Risk factors include age over 40 years, obesity, smoking, alcohol excess and immunosuppression.
- Testing for anti-HBs is only recommended for those at risk of occupational exposure (i.e. Healthcare workers) and patients with chronic kidney disease. In these patients **anti-HBs levels** should be **checked 1-4 months after** primary immunisation.
- The table below shows how to interpret anti-HBs levels:

| Anti-HBs level (mIU/ml) | Response |
|---|---|
| > 100 | Indicates adequate response, no further testing required. Should still receive booster at 5 years. |
| 10 – 100 | Suboptimal response - one additional vaccine dose should be given. If immunocompetent no further testing is required. |
| < 10 | Non-responder. Test for current or past infection. Give further vaccine course (i.e. 3 doses again) with testing following. If still fails to respond then HBIG would be required for protection if exposed to the virus. |

**Complications** of hepatitis B infection:

- Acute fulminant hepatitis with acute liver failure (1%)
- Chronic hepatitis (5-10%)
- Hepatocellular carcinoma
- Membranous glomerulonephritis
- Cryoglobulinaemia
- Polyarteritis nodosa

Deterioration in patient with hepatitis B >>>>- ? hepatocellular carcinoma

## Management of hepatitis B:

- **Pegylated interferon-alpha** used to be the only treatment available. It reduces viral replication in up to 30% of chronic carriers. A better response is predicted by being female, < 50 years old, low HBV DNA levels, non-Asian, HIV negative, high degree of inflammation on liver biopsy. It is used in **chronic** HBV with **positive HBeAg.**
- However due to the **side-effects** of pegylated interferon it is now used **less** commonly in clinical practice.
- Interferon **cannot** be used in **decompensated** liver cases (ascites, portal hypertension, low serum albumin, high INR, etc.) as it can **initially worsen hepatic decompensation**.
- **Oral antiviral** medication is increasingly used with an aim to suppress viral replication (not in dissimilar way to treating HIV patients) Examples include: **Entecavir**, **Tenofovir** and **Lamivudine.**
- **Entecavir** or **Tenofovir** would be **the most appropriate drug** choice. In certain circumstances the two may even be combined. Their use in this situation is not risk free and may precipitate a lactic acidosis so careful monitoring is required.

- They are **second** line to interferon for **compensated** liver disease, but with hepatic **decompensation**, they are a reasonable **first** choice.
- **Lamivudine** alone is safe in **decompensated** HBV infection however it is **no** longer the drug of choice in this setting as entecavir and tenofovir give more rapid control of HBV DNA levels. Additionally lamivudine resistance may be pre-existent or induced.
- **Liver biopsy** is **only** indicated in patients who have **elevated liver enzymes** and **positive HBeAg**.
- Antiviral therapy of HBV is indicated for **progressive liver disease** as manifested by **histological** evidence of active **inflammation** ± **fibrosis**. The best results are seen in **HBeAg positive** patient with **elevated liver enzymes**.
- Guidance suggests in a case of HBV, it is worth offering **HIV** and **HCV** tests as exposure to HBV may well indicate exposure to other blood borne viruses.

## Hepatitis B and pregnancy

### Basics:

- **All** pregnant women are offered screening for hepatitis B.
- **Without** intervention the **vertical** transmission rate is around **20%**, which increases to **90%** if the woman is positive for **HBeAg**.
- **HBeAg** is present in the **acute** phase and indicates a **highly infectious state.**
- **Babies** born to mothers who are chronically infected with hepatitis B or to mothers who've had acute hepatitis B during pregnancy should receive a complete course of **vaccination** + hepatitis B **immunoglobulin.**
- Studies are currently evaluating the role of **oral** antiviral treatment (e.g. **Lamivudine**) in the **latter** part of pregnancy.
- There is **little** evidence to suggest **caesarean** section reduces vertical transmission rates.
- Hepatitis B **cannot** be transmitted via **breastfeeding** (in contrast to **HIV**).

**The most common causes of an acute severe liver injury in a young woman are:**

- **Viruses** (including HAV, HBV).
- **Drugs** (particularly **paracetamol** overdose).
- **Ischemic hepatitis.**
- **Autoimmune hepatitis.**
- **Hepatic vein thrombosis (Budd-Chiari syndrome [BCS])**: (often precipitated by pregnancy or oral contraceptive pill [OCP] use or Antiphospholipid syndrome).

The presence of liver failure, ankle oedema, and an exudative ascites do not help differentiate between these aetiologies.

**Tender hepatomegaly** is one of the hallmarks of **BCS**.

# Hepatitis C

**NICE GUIDELINES 2018**

Hepatitis C is likely to become a significant public health problem in the UK in the next decade.
It is thought around 200,000 people are chronically infected with the virus.
At risk groups include intravenous drug users and patients who received a blood transfusion prior to 1991 (e.g., haemophiliacs).

## Pathophysiology

- hepatitis C is an **RNA flavivirus**
- incubation period: **6-9 weeks**

## Transmission:

- The risk of transmission during a needle stick injury is about **2%**
- The risk of transmitting the virus during sexual intercourse is probably less than **5%**
- The vertical transmission rate from mother to child is about **6%**
- Elective caesarean section **dose not** reduce the risk of transmission.
- **Breast** feeding is **not** contraindicated in mothers with hepatitis C.
- Ribavirin is **teratogenic** and there is little clinical data about how well this or interferon is tolerated in pregnancy.
- Children under 1 year can be tested for hepatitis C, but as there is transmission of the antibodies from the mother they may test **positive** with respect to serology in the first year.

About **6** out of every **100** infants born to **HCV**-infected **women** become **infected**. This occurs at the time of **birth** and there is **no** way of preventing this.

## Features:

- After exposure to the hepatitis C virus **less than 20%** of patients develop an **acute** hepatitis.
- Around **85%** of **acute** hepatitis C infections lead to **chronic** infection.
- Acute hepatitis C has a good response to treatment if started early.
- **Chronic hepatitis C is a very common cause of minor elevations in serum transaminases.**
    - **Other liver function tests can be entirely normal**

## Complications:

- **Chronic infection (80-85%)** - only 15-20% of patients will clear the virus after an acute infection and **hence the majority will develop chronic hepatitis C.**
- Cirrhosis **(20-30%** of those with chronic disease)
- Hepatocellular cancer
- **Cryoglobulinaemia**

## Extra-hepatic associations with HCV:

- **Sjogren's** syndrome.
- **Porphyria cutanea tarda**, rather than acute intermittent porphyria.
- **Lichen planus**, rather than lichen sclerosis.
- **Cryoglobulinaemia** (mixed essential type).
- **Lymphoma**, rather than leukaemia
- **Myeloma** and **monoclonal gammopathies,** rather than Waldenström macroglobulinaemia.

## Management of chronic infection:

- Chronic hepatitis C is defined as infection that lasts for more than 6 months.
- treatment depends on the viral genotype - this should be tested prior to treatment
- the management of hepatitis C has advanced rapidly in recent years resulting in clearance rates of around 95%.
- **Interferon based treatments are no longer recommended**
- **the aim of treatment is sustained virological response (SVR), defined as undetectable serum HCV RNA six months after the end of therapy**

## Currently:

**1. a combination of protease inhibitors (e.g., daclatasvir + sofosbuvir or sofosbuvir + simeprevir)** with or without ribavirin are used

- **HCV genotype** will give guidance to the **length of treatment** and **response rate**:

- Those with genotype **2** and **3** can achieve **SVR (SUSTAINED VIROLOGY RESPONSE)** after **24** weeks, as they have a far **better** response to treatment than genotype 1 & 4.
- In genotype **1** and **4**, antiviral is continued for **48** weeks due to **lower** response rate.

- **Liver biopsy** provides histological activity indices to help quantify the degree of inflammation and fibrosis and is generally ***only*** indicated in those with genotype 1 and 4, as treatment is longer.

### 2. (Sofosbuvir–velpatasvir–voxilaprevir) for treating all genotypes

- **Clinical trials show that sofosbuvir–velpatasvir–voxilaprevir is effective for treating all genotypes.**
- Sofosbuvir–velpatasvir–voxilaprevir is recommended as an option for treating chronic hepatitis C in adults, only if it is used as specified as following:
  - The recommended dose is 1 tablet taken orally once daily.
  - Each tablet contains 400 mg sofosbuvir, 100 mg velpatasvir and 100 mg voxilaprevir.
  - Treatment duration is 8 or 12 weeks depending on cirrhosis status and whether the person has had previous treatment with direct-acting antivirals.

Please see the summary of product characteristics for more details.

**N.B**

- Liver cirrhosis >>>>will develop in around 20-30% of patients over 20-30 years.
- Presence of HCV Ab indicates old exposure to the virus, if detected a viral RNA load is required to determine whether there is active infection.

**Extrahepatic manifestations of chronic HCV infection: (PEN-DG)**

- **Porphyria cutanea tarda**
- **Essential mixed crvoglobulinemia**
- **Non-Hodgkin's lymphoma**
- **Diabetes mellitus**
- **Glomerulonephritis**

Hepatitis C infection is strongly associated with **mixed essential cryoglobulinaemia** which may produce **mesangiocapillary** (also known as **membranoproliferative**) glomerulonephritis.

This condition is associated with renal impairment, systemic vasculitic manifestations (including neuropathy, skin manifestations) and arterial thrombosis.

## Hepatitis D

- Hepatitis D is a **single stranded RNA delta virus**
- It is an incomplete RNA virus that requires hepatitis B surface antigen to complete its replication and transmission cycle.
- It is **transmitted in a similar fashion to hepatitis B** (exchange of bodily fluids) and patients may be infected with hepatitis B and hepatitis D at the same time.
- **Co-infection:** Hepatitis B and Hepatitis D infection at the same time.
- **Superinfection:** A hepatitis B surface antigen positive patient subsequently develops a hepatitis D infection.
- Superinfection is associated with high risk of fulminant hepatitis, chronic hepatitis status and cirrhosis.
- Diagnosis is made via reverse polymerase chain reaction of hepatitis D RNA.
- **Interferon** is currently used as treatment, but with a poor evidence base.

## Hepatitis E

**Overview:**

- RNA virus.
- Spread by the **faecal-oral route, incubation period = 3-8 weeks.**
- Common in Central and South-East Asia, North and West Africa, and in Mexico.
- Causes a similar disease to hepatitis A, but carries a significant mortality (about 20%) during pregnancy.
- Does not cause chronic disease
- A vaccine is currently in development, but is not yet in widespread use.

**NB:** Male homosexuality is a recognized risk factor for hepatitis A infection, anal intercourse is a likely route of enteral transmission.

## Chronic active hepatitis

20% of patients with HBV will develop chronic active hepatitis, whereas the incidence is **higher 50%** in **HCV** infection.

It is usually due to old history of blood transfusion.

The aminotransferase and bilirubin are **mildly raised.**

The histological landmark is **piecemeal necrosis**.

### Causes of chronic active hepatitis:

- Viral.
- Autoimmune (anti LKM ab).
- Drugs (Aldomet, INH).
- Alpha-1-antitrypsin deficiency.
- Ulcerative colitis (UC)

## Acute liver failure

Acute liver failure describes the rapid onset of hepatocellular dysfunction leading to a variety of systemic complications.

### Causes

- paracetamol overdose
- alcohol
- viral hepatitis (usually A or B)
- acute fatty liver of pregnancy

### Features

- jaundice
- coagulopathy: raised prothrombin time
- hypoalbuminemia
- hepatic encephalopathy
- renal failure is common ('hepatorenal syndrome')

**Remember that 'liver function tests' do not always accurately reflect the synthetic function of the liver.**
**This is best assessed by looking at the prothrombin time and albumin level.**
**ENZYMATIC FUNCTION IS ASSESSED BY ALT AND AST.**

# liver cirrhosis

## Causes:

- alcohol
- non-alcoholic fatty liver disease (NAFLD)
- viral hepatitis (B and C)

## Features

### Abdominal symptoms

- Hepatomegaly (possibly causing RUQ pain)
- Splenomegaly
- **Ascites**
- **Portal hypertension(varices)** = Hepatic intrasinusoidal pressure is elevated

### Cardiac

- Cardiac output is often elevated
- The cardiomyopathy of **alcoholism** is a dilated or congestive form.
- **Dilated cardiomyopathy**
- hyper dynamic circulation
- Systemic vasodilatation
- LOW vascular resistance,
- Increased plasma volume >> low serum sodium.
- Most patients have sodium and water retention.

### Hormone disorders

- Hypoestrogenism
  - **Gynecomastia,** decreased body hair (e.g., chest hair)
  - **Hypogonadism** (testicular atrophy)
  - **Reduced libido**, erectile dysfunction, infertility
- Amenorrhea.

## Investigations

- traditionally a liver biopsy was used.
  - This procedure is however associated with adverse effects such as bleeding and pain
- other techniques such as transient elastography and acoustic radiation force impulse imaging
- for patients with NAFLD, NICE recommend using the enhanced liver fibrosis score to screen for patients who need further testing

### What is transient elastography?

- brand name 'Fibroscan'

- uses a 50-MHz wave is passed into the liver from a small transducer on the end of an ultrasound probe
- measures the 'stiffness' of the liver which is a proxy for fibrosis

**In terms of screening** for cirrhosis NICE made a specific recommendation, suggesting to offer transient elastography to:

- people with hepatitis C virus infection
- men who drink over 50 units of alcohol per week and women who drink over 35 units of alcohol per week and have done so for several months
- people diagnosed with alcohol-related liver disease

### Further investigations

- NICE recommend doing an upper endoscopy to check for varices in patients with a new diagnosis of cirrhosis
- liver ultrasound every 6 months (+/- alpha-feto protein) to check for hepatocellular cancer
- ALT is more specific than other liver enzymes in diagnosing hepatic injury.
- Increase plasma volume
- ↓↓ serum sodium
    - Patients with cirrhosis are frequently hyponatraemic.
- Urinary sodium concentration is usually less than 10 mmol/l
- Thrombocytopenia is a common finding in chronic liver disease.

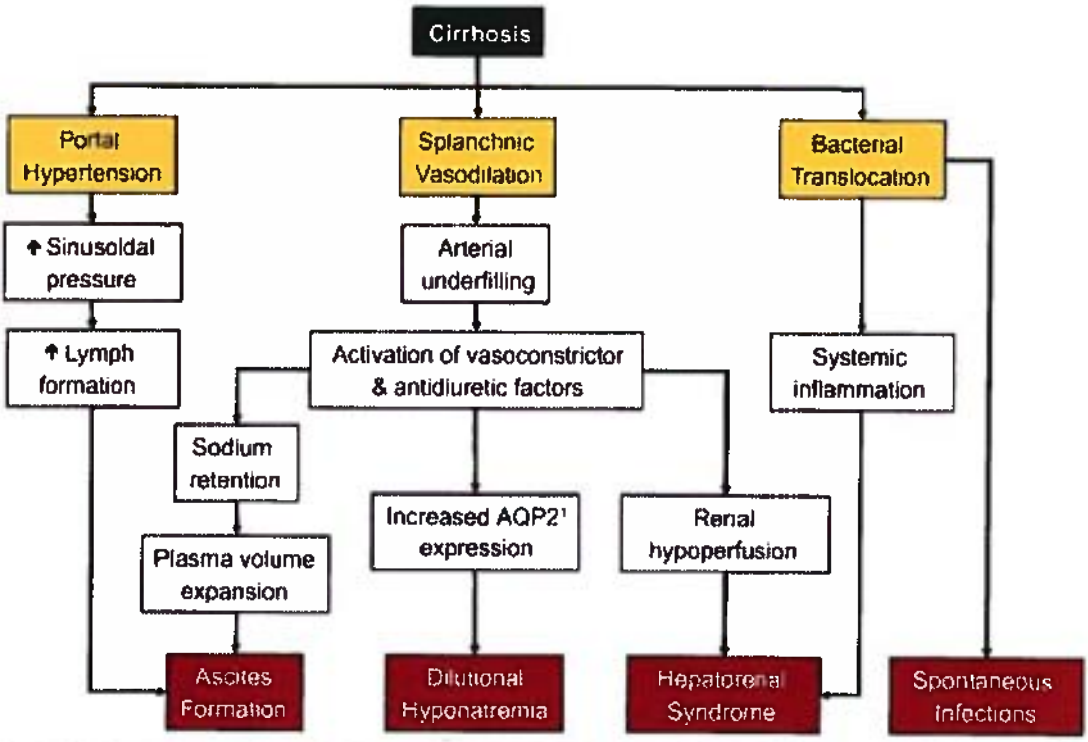
### Scoring systems for liver cirrhosis

- For many years the Child-Pugh classification was used to classify the severity of liver cirrhosis.
- However, in recent years the Model for End-Stage Liver Disease (MELD) has been increasingly used, particularly patients who are on a liver transplant waiting list
- **Child-Pugh classification**
- Summation of the scores allows the severity to be graded either A, B or C:
    - **< 7 = A**
    - **7-9 = B**
    - **9 = C**

**It is a scoring system to assess the severity of liver cirrhosis.**

| Score | 1 | 2 | 3 |
|---|---|---|---|
| **Bilirubin (µmol/l)** | <34 | 34-50 | >50 |
| **Albumin (g/l)** | >35 | 28-35 | <28 |
| **Prothrombin time, prolonged by (s)** | <4 | 4-6 | >6 |
| **Encephalopathy** | none | mild | marked |
| **Ascites** | none | mild | marked |

SUMMARY OF mechanism of development of different syndromes related to liver cirrhosis




**EX**: Pt. with CLD and ascites on diuretics with serum Na 115 mmol/L >>> **Stop diuretics and give normal saline.**

Esophageal varices in the patient secondary to her cirrhosis and portal hypertension.

Palmar erythema in a man with cirrhosis secondary to alcoholism

Spider angioma on the face of a woman with cirrhosis secondary to chronic hepatitis C.

# Ascites

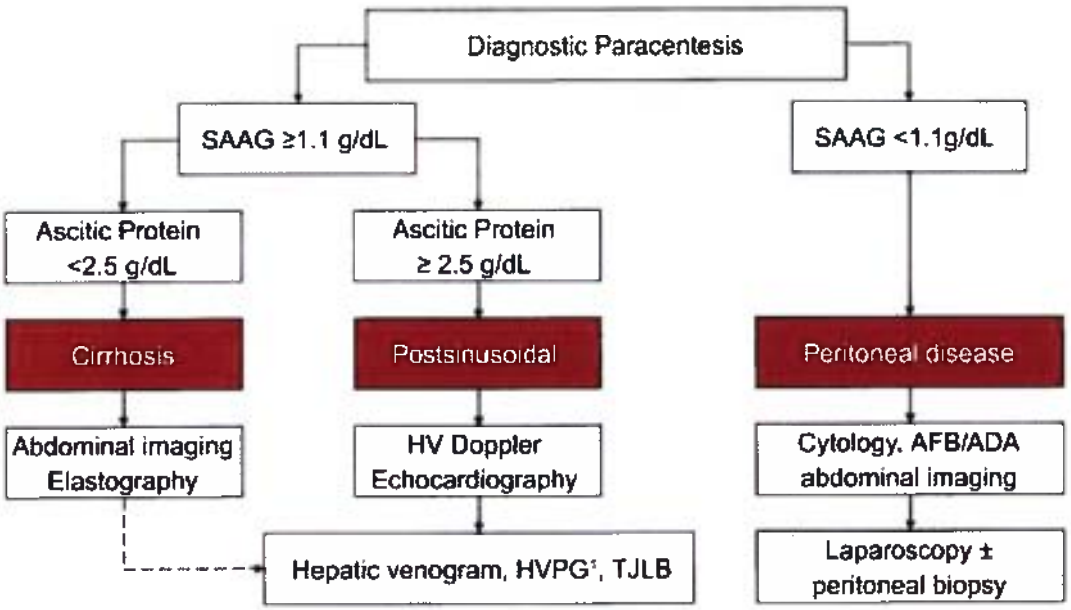
## It is the abnormal accumulation of fluid in the abdomen.

- The serum ascites albumin gradient (SAAG) is the most sensitive and specific method of categorising ascites.
- To calculate the ascitic fluid albumin should be subtracted from the serum albumin.
- A value that is ≥11 g/L (high SAAG) indicates a transudate
  - less than 11g/l (low SAAG) indicates an exudate

Tense ascites in a woman with cirrhosis from her alcoholism. An umbilical hernia is also seen from the increased intra- abdominal pressure.

**The causes of ascites can be grouped into those with a serum-ascites albumin gradient (SAAG) <11 g/L or a gradient >11g/L as per the table below:**

| SAAG > 11g/L (indicates portal hypertension) | SAAG <11g/L |
|---|---|
| **Liver disorders are the most common cause**<br>• cirrhosis/alcoholic liver disease<br>• acute liver failure<br>• liver metastases<br>**Cardiac**<br>• right heart failure<br>• constrictive pericarditis<br>**Other causes**<br>• Budd-Chiari syndrome<br>• portal vein thrombosis<br>• veno-occlusive disease<br>• myxoedema | **Hypoalbuminaemia**<br>• **nephrotic syndrome**<br>• **severe malnutrition (e.g. Kwashiorkor)**<br>**Malignancy**<br>• **peritoneal carcinomatosis**<br>**Infections**<br>• **tuberculous peritonitis**<br>**Other causes**<br>• **pancreatitisis**<br>• **bowel obstruction**<br>• **biliary ascites**<br>• **postoperative lymphatic leak**<br>• **serositis in connective tissue diseases** |



## Treatment

### Large, symptomatic ascites

- **(therapeutic abdominal paracentesis)**
- drainage if tense ascites
- large-volume paracentesis for the treatment of ascites requires albumin 'cover' >> reduces paracentesis-induced circulatory dysfunction and mortality
- paracentesis induced circulatory dysfunction can occur due to large volume paracentesis (> 5 litres).

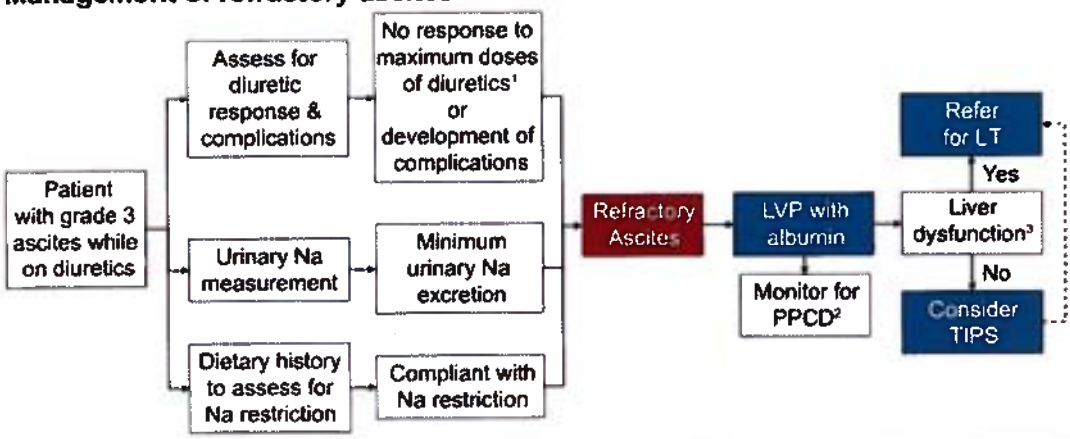
It is associated with a high rate of ascites recurrence, development of hepatorenal syndrome, dilutional hyponatraemia, and high mortality rate

- **Paracentesis is less likely to be successful if the patient has peripheral oedema**
- Paracentesis is relatively contraindicated if the patient is encephalopathic

### Not large, asymptomatic ascites

- Dietary salt restriction (to no more than 90 mmol/day) + spironolactone
- **The initial management would be spironolactone**
  - Initial dose of spironolactone is 100 mg/day and may be titrated up to 400 mg/day.
  - Once the maximum dose of spironolactone has been reached furosemide can be added
  - Doses of furosemide are advised start at 40 mg/day titrating up to 160 mg/day as tolerated or needed.
  - Furosemide alone has poor efficacy in cirrhosis.
  - Spironolactone is more effective than furosemide **because** the site of sodium retention in cirrhosis is the distal nephron
  - The ideal weight loss is 0.5 kg/day

**Management of refractory ascites**


Patient with grade 3 ascites while on diuretics
Assess for diuretic response & complications
Urinary Na measurement
Dietary history to assess for Na restriction
No response to maximum doses of diuretics¹ or development of complications
Minimum urinary Na excretion
Compliant with Na restriction
Refractory Ascites
LVP with albumin
Monitor for PPCD²
Liver dysfunction³
Yes
No
Refer for LT
Consider TIPS

**Management of hyponatraemia in patients with chronic liver disease and ascites:**

- serum sodium is 126-135 mmol/L >> • No specific intervention other than monitoring
- serum sodium is 121-125 mmol/L + normal creatinine >> Reduce diuretics
- serum sodium is 121-125 mmol/L + high creatinine >> Stop diuretics + give volume expansion
  - **Serum sodium is ≤120 mmol/L >> Stop diuretics + give volume expansion with colloid or normal saline.**

**Management of hypoproteinaemia in patients with chronic liver disease**

- Cirrhotic ascites has significantly lower protein and complement levels than non-cirrhotic ascites.
- Indications for the use of albumin in cirrhosis:
  - post-paracentesis circulatory dysfunction,
  - spontaneous bacterial peritonitis
  - Hepatorenal syndrome.
- **20% salt poor albumin (human albumin solution)**
  - The salt-poor preparation of albumin is particularly important in this scenario as high salt load will encourage fluid to shift into the extravascular compartment resulting in fluid overload.
- prophylactic antibiotics to reduce the risk of spontaneous bacterial peritonitis.
  - Offer prophylactic oral ciprofloxacin or norfloxacin for people with cirrhosis and ascites with an ascitic protein of 15 g/litre or less, until the ascites has resolved'
- a Transjugular intrahepatic portosystemic shunt (TIPS) may be considered in some patients

**What is the most characteristic physiological activity that retains sodium in the face of salt and water overload?**

- **Arterial underfilling**

  In liver cirrhosis, **arterial vasodilatation** due to nitric oxide overactivity, coupled with hypoalbuminemia, which drives low colloid osmotic pressure, leads to arterial underfilling.

**Meig's syndrome >> ovarian fibroma associated with a pleural effusion and ascites**

| Complications of cirrhosis | Albumin use | |
|---|---|---|
| PPCD | 8 g/l of ascites removed (above 5 l) | According to guidelines |
| SBP | 1.5 g/kg on day 1 and 1g/kg on day 3 (in association with antibiotics) | |
| HRS | Loading and maintenance dose + terlipressin untill HRS resolution | |
| Non-SBP Infections | Improvement in renal and circulatory function (no effect on survival, only one study available) | Controversial indications (more studies needed) |
| HE | Only two discordant studies available (effect on oxidative stress) | |
| Ascites | Not yet enough evidence for the utility of chronic use *(ANSWER Study currently ongoing)* | |
| ACLF | Albumin dialysis (MARS and Prometheus systems) | |

Summary table of the current uses of albumin in hepatology, according to the main international guidelines and looking at future perspectives (**PPCD**: post-paracentesis circulatory dysfunction; **SBP**: spontaneous bacterial peritonitis; **HRS**: hepatorenal syndrome; **HE**: hepatic encephalopathy; **ACLF**: acute-on-chronic liver failure).

**NB: Abdominal Tuberculosis** should always be suspected in the severely malnourished patient and is difficult to diagnose, SAAG < 11 gm/L, high ascetic WBC mainly lymphocytes, should do >>> **Laparoscopy** and **peritoneal biopsy** is diagnostic in 95% of cases.

# Spontaneous bacterial peritonitis

SBP is a form of peritonitis usually seen in patients with ascites secondary to liver cirrhosis.
SBP occurs in around **8%** of **cirrhotic patients with ascites**.
SBP has **poor** prognostic significance with **high mortality** as a **one**-year survival after a diagnosis of between **30-50%** and **recurs** in **70%** of patients **within one year**.

An **episode** of SBP carries a 2-year mortality rate of **50%**.

It is, as the name suggests a spontaneous event that is not a consequence of intestinal perforation.
It is speculated that the infective organism may leak into the ascitic fluid via the blood or from intestinal overgrowth.
Organisms should be cultured by directly collecting into blood culture bottles.
It is **typically caused by aerobic gram-negative bacteria.**
Hence, antibiotics such as co-amoxiclav, **Tazoscin** or ciprofloxacin are typically used as first line treatment.

**E. coli, Klebsiella** and **Enterococci** should be considered **aerobic** organisms. They are more precisely defined as **facultative anaerobes**, that is to say they reproduce best in aerobic conditions but can also reproduce in anaerobic conditions.

**SBP** is usually the result of infection with a **single organism**, almost invariably **Gram negative**.
But the **polymicrobial** nature (**both** Gm +ve and Gm – ve) of this infection makes **perforated abdominal viscera** the most likely diagnosis.

## Features

- ascites
- abdominal pain
- fever

## Diagnosis:

- paracentesis: **neutrophil count > 250 cells/ul**
- high serum ascites albumin gradient (SAAG) (>11 g/L)
- White cells will be **predominantly neutrophils (>500 WBCs/mm3and >50% neutrophils).**

## Management:

- **intravenous cefotaxime** is usually given
- other option: **IV piperacillin-tazobactam**
- It is important to start antibiotics promptly pending the results of an ascitic analysis

**Antibiotic prophylaxis should be given to patients with ascites if:**

- patients who have had an episode of SBP
- patients with fluid protein <15 g/l and either Child-Pugh score of at least 9 or hepatorenal syndrome
- NICE recommend: 'Offer prophylactic **oral ciprofloxacin or norfloxacin** for people with cirrhosis and ascites with an ascitic protein of 15 g/litre or less until the ascites has resolved'

## Prognosis

- Alcoholic liver disease is a marker of poor prognosis in SBP.
- Has poor prognostic significance with a one-year survival after a diagnosis of between 30-50%.
  - **An episode of spontaneous bacterial peritonitis carries a two-year mortality rate of 50%.**

**Alcoholic liver disease is a marker of poor prognosis in SBP.**

Spontaneous bacterial peritonitis (SBP) >>> IV cefotaxime

## Differential diagnosis

- **High SAAG (>11 g/L)** and are differentiated from each other on the basis of white cell count, Gram stain and culture results
- **Pancreatic ascites** (e.g., Acute pancreatitis)
  - Elevated fluid amylase helps confirm this
- **Secondary bacterial peritonitis** (ruptured viscus or loculated abscess). • Lactate dehydrogenase >225mU/L, glucose 1g/dL and **multiple organisms on gram stain suggest secondary bacterial peritonitis**
- **Chylous ascites**
  - A high level of triglycerides confirms chylous ascites.
- Elevated bilirubin level suggests biliary or gut perforation.
- Elevated amylase level suggests pancreatitis or gut

# Hepatic encephalopathy

Hepatic encephalopathy may be seen in liver disease of any cause. The aetiology is not fully understood but is thought to include excess absorption of ammonia and glutamine from bacterial breakdown of proteins in the gut.

## Features

- confusion, altered GCS (see below)
- asterix: 'liver flap',
  - arrhythmic negative myoclonus .
  - **hepatic encephalopathy is unlikely to be present if a liver flap (asterixis) cannot be detected**
- constructional apraxia: inability to draw a 5-pointed star
- triphasic slow waves on EEG
- raised ammonia level (not commonly measured anymore)

### There are 5 grades of hepatic encephalopathy:

**Grade 0:** include **minimal** alterations and impairment of executive function.
**Grade 2:** patients are **drowsy**, is associated with **sleep** abnormalities (typically sleep inversion) and changes to **behaviour** and **personality** (irritability, poor concentration).
**Grade 2:** **Lethargy**, **apathy** and **drowsiness** are features of grade 2.
**Grade 3:** depressed conscious levels (but arousable).
**Grade 4:** patients are **comatose** with no response to painful stimuli.

### Precipitating factors:

- infection e.g., spontaneous bacterial peritonitis
- GI bleeding.
- post trans jugular intrahepatic portosystemic shunt
- constipation.
- drugs: sedatives, diuretics
- hypokalemia
- renal failure
- increased dietary protein (uncommon)

## Management:

- treat any underlying precipitating cause
- NICE recommend **lactulose first-line, with the addition of rifaximin** for the secondary prophylaxis of hepatic encephalopathy
- antibiotics such as rifaximin are thought to modulate the gut flora resulting in decreased ammonia production
- **other options** include embolization of portosystemic shunts and liver transplantation in selected patients

**Lactulose:**

- It is an osmotic laxative; it is used in patients with cirrhosis/hepatic encephalopathy to **limit the proliferation** of **ammonia-forming gut organisms** and **increase the clearance of protein load in the gut.**
- Dose of lactulose **30-50 ml / 6hrs** orally or via nasogastric tube.
- It causes **hypomagnesaemia** associated with diarrhoea.
- It is **not absorbed** It does not affect the absorption of spironolactone and
- It may be used in diabetics
- **TIPS:**
- Pt with chronic **HCV** infection + **renal failure** + significant **proteinuria** + high urine Na + relative hypertension >>> **cryoglobulinaemia**

There is **little** evidence for the role of **protein restriction** in hepatic encephalopathy. This may exacerbate the condition as these patients are often malnourished.

## Portal hypertension

The liver receives approximately 1500 ml of blood each minute, **two-thirds of which is provided by the portal vein.**

### Definition:

- abnormally high pressure in the hepatic portal vein (hepatic venous pressure gradient of 10 mm Hg or more).
- Portal hypertension is present when the wedged hepatic vein pressure is more than 5 mmHg higher than the inferior vena cava pressure.

### Mechanism of porto-systemic collaterals

- Because the **veins in the portal system lack valves**, increased resistance to flow at any point between the splanchnic venules and the heart will increase the pressure in all vessels on the intestine site of the obstruction.
- This is manifest clinically by the development of porto-systemic collaterals (oesophageal varices), splenomegaly and/or ascites.

| Site ofAnastomosis | Clinical Sign | Portal ↔ Systemic |
|---|---|---|
| Esophagus | Esophageal varices | Left gastric ↔ esophageal |
| Umbilicus | Caput medusae | Paraumbilical ↔ superficial and inferior epigastric |
| Rectum | Anorectal varices (sometimes referred to as internal hemorrhoids though they are different) | Superior rectal ↔ middle and inferior rectal |

## Causes

Vascular resistance and blood flow are 2 important factors in its development

**Pre-hepatic - (pre-sinusoidal) blockage of the portal vein before the liver**

- Congenital atresia or stenosis.
- **Portal vein thrombosis** (idiopathic, **umbilical and portal sepsis**, malignancy, hypercoagulable states, pancreatitis).
  - **Longstanding portal vein thrombosis is a well recognised complication in premature neonates due to cannulation of the umbilical vein during neonatal intensive care.**
    - **the best initial investigation is → Ultrasound with Doppler**
- Splenic vein thrombosis.
- Extrinsic compression - eg, tumours.

**Hepatic (sinusoidal)**

- Cirrhosis. **(the most common cause)**
- Chronic hepatitis.
- Schistosomiasis.
- Myeloproliferative diseases.
- Idiopathic portal hypertension.
- Granulomata - eg, sarcoid.
- Toxins (arsenic, vinyl chloride).

**Post-hepatic - (post-sinusoidal) blockage of hepatic veins or venules**

- Budd-Chiari syndrome (hepatic vein obstruction).
- Constrictive pericarditis.
- Right heart failure onia level (not commonly measured anymore)
- **Wedged hepatic venous pressure**
  - The pressure recorded by a catheter wedged in a hepatic vein.
  - It reflects the portal venous pressure in the hepatic sinusoids.
  - **↑↑ in sinusoidal and post-sinusoidal portal hypertension**
  - Remains normal in pre-sinusoidal portal hypertension.

**Complications of portal hypertension:**

- Haematemesis or melaena - suggest bleeding varices.
- Lethargy, irritability and changes in sleep pattern - suggest encephalopathy.
- Increased abdominal girth, weight gain - suggest ascites.
- Abdominal pain and fever - suggest spontaneous bacterial peritonitis.
- Pulmonary involvement is common in patients with portal hypertension

**Trans-jugular intrahepatic porto-systemic shunt (TIPSS)**

- **Indications are:**
  - Diuretic resistant ascites (**Intractable ascites**)
  - Intractable portal hypertensive bleeding and
  - Hepato-renal failure.

- **contraindications to shunting:**
  - Severe hepatic encephalopathy
  - Severe heart failure
  - Septicaemia

## Hepatorenal syndrome (HRS)

**The diagnostic criteria for HRS:** **Acute** or **chronic** hepatic disease with advanced **hepatic cell failure** and **portal hypertension**.

- Serum **creatinine** concentration **> 133 Mmol/L** that progresses over days to weeks.
- **Absence of any other apparent cause** for the renal disease like shock, sepsis, nephrotoxic drugs, and the absence of US finding of obstruction of parenchymal renal disease, or abdomen compartmental syndrome.
- It is important to **exclude SBP**, which is complicated with acute renal failure.
- **Urinary Na below 10 mEq/l** (off diuretics).
- **Urinary protein excretion below 500 mg/day.**
- **Lack of improvement** in renal function after volume expansion with 2 litres of normal saline.

**Hepatorenal syndrome has been categorized into two types:**

| Type 1 HRS | Type 2 HRS |
|---|---|
| ➢ Rapidly progressive.<br>➢ Doubling of serum Creatinine to > 221 µmol/L or a halving of the Creatinine clearance to less than 20 ml/min over a period of less than 2 weeks.<br>➢ Very poor prognosis. | ➢ Slowly progressive.<br>➢ **characterised by a moderate and stable reduction in renal function, hypotension and diuretic resistance.**<br>➢ Prognosis poor, but patients may live for longer. |

The management of hepatorenal syndrome (HRS) is notoriously difficult.

The ideal treatment is liver transplantation but patients are often too unwell to have surgery and there is a shortage of donors.

### Management options:

- **Vasopressin** V1 receptors agonist, for example **terlipressin**, have a growing evidence base supporting their use. They work by causing vasoconstriction of the splanchnic circulation, which may reverse the early splanchnic vasodilatation seen in HRS.
- **Volume expansion with 20% albumin** (1.5 gm/ Kg of body weight at diagnosis and 1.0 gm/ kg 48 hours later).

- **Antibiotics,** has been shown in RCT to markedly reduce the risk of hepatorenal syndrome.
- **Transjugular intrahepatic portosystemic shunt** (**TIPS**).
- **Liver transplantation.**

## Hepatopulmonary syndrome (HPS)

This is characterised by an **oxygenation defect** induced by **pulmonary vascular dilatation** in patients with liver cirrhosis or portal hypertension.

This oxygenation defect consists of a **wide alveolar-arterial gradient** (AAG) (>15mmHg). The vascular dilatation is thought to be induced by increased pulmonary levels of nitric oxide. It is seen in **15-30% of patients with cirrhosis** and is a poor prognostic indicator.

Most patients with hepatopulmonary syndrome are **asymptomatic** or have dyspnoea with an insidious onset. Dyspnoea whilst **standing** (**platypnoea**) and hypoxemia exacerbated by being **upright** (**orthodeoxia**) are characteristic, and are thought to be due to the **predominance** of **vascular dilatation** in the **lung bases**. Blood flow to these areas is increased in the upright position.

Desaturation during sleep is also often seen as are clubbing and cyanosis.

**Contrast-enhanced transthoracic echocardiography** is the best test to demonstrate **intrapulmonary vascular dilatation**. It can also exclude **intracardiac shunting** which may result in similar signs and symptoms to hepatopulmonary syndrome.
This is performed by injecting agitated saline IV during transthoracic echocardiography.

- In a **normal** subject microbubbles are visualised in the right ventricle within seconds, which are then absorbed in the alveoli.
- Immediate visualisation in the **left** ventricle (within 3 cardiac cycles) indicates **intracardiac** shunting.
- Delayed visualisation in the left ventricle (3-6 cardiac cycles) is diagnostic of **intrapulmonary** shunting.

Chest radiographs can be normal or show non-specific interstitial changes.

ABGs should be taken in the sitting position to grade the severity of the condition based on the degree of hypoxemia.

**Liver transplantation** is the only proven beneficial available treatment, with 85% of patients showing resolution or significant improvement in gas exchange postoperatively.

## Hyponatraemia in Patients with chronic liver disease

Patients with chronic liver disease and ascites often develop hyponatraemia, the management of which can be difficult.

Diuretic therapy for the management of ascites often contributes to the hyponatraemia.

- **The British Society of Gastroenterology guidelines** suggest that:
  - **serum sodium is ≤120 mmol/L >> normal saline + stop diuretic**
  - serum sodium is 126-135 mmol/L >> No intervention other than careful monitoring.
  - serum sodium is 121-125 mmol/L + normal serum creatinine >> reduce diuretics or stop it if necessary
  - serum sodium is 121-125 mmol/L +↑↑ serum creatinine >> volume expansion + stop diuretics
  - fluid restriction should only be used in patients who are clinically euvolaemic, not on diuretics and have severe hyponatraemia with a normal serum creatinine.

## Gilbert's syndrome

Gilbert's syndrome is an **autosomal recessive** condition (although the exact mode of inheritance is still a matter of debate)
It is of defective bilirubin **conjugation** due to a **deficiency of UDP glucuronyl transferase.**
Gilbert's is the **most common** condition causing **mild isolated hyperbilirubinaemia** with all the other **LFTs** are completely **normal.**
The prevalence is approximately **2-7%** in the general population.
It is often diagnosed incidentally during routine per-employee check-up.
The jaundice is usually **exacerbated** by periods of **fasting**, **alcohol**, **acute illness** even like **sore throat** also by **oestrogen** and it is **improved** by low dose barbiturates.

**Features:**

- **Unconjugated** hyperbilinaemia (i.e. **not in urine).**
- Jaundice **may only** be seen during an **intercurrent** illness.

**Investigation:** rise in bilirubin provoked by prolonged fasting or **IV nicotinic acid.**

### Management:

- **No** treatment required.
- If severe jaundice (which is rare), phenobarbitone can rapidly decrease unconjugated serum bilirubin levels.

**EX**: A 26-year-old presents in the first trimester of her first pregnancy she feels well. Blood tests show a bilirubin of 40 µmol/L (1-22); the other LFTs are completely normal >>> **Gilbert's syndrome.**
**EX**: Morning sickness and pruritus are common in **pregnant** women. An **ALP** of **160** U/l which is **normal** in a **pregnant** woman leaving the only abnormal result being the raised **bilirubin** (which usually falls in pregnancy). The most likely diagnosis is therefore **Gilbert's syndrome**.

## Rotor syndrome

- autosomal recessive
- defect in the hepatic uptake and storage of bilirubin
- benign

| Unconjugated hyperbilirubinaemia (indirect) | conjugated hyperbilirubinaemia (Direct) |
|---|---|
| • **Water-insoluble**<br>• **so not pass to urine (normal colour).**<br>  ○ **Gilbert's syndrome**<br>  ○ **Crigler-Najjar syndrome** | • **it is water-soluble**<br>• **pass to urine (dark).**<br>  ○ **Dubin-Johnson syndrome**<br>  ○ **Rotor syndrome** |

## Crigler-Najjar syndrome

### type 1

- Condition of Absent UDP-glucuronyl transferase.
- This condition presents early in life with jaundice, increased unconjugated bilirubin and kernicterus.
- This disease is life threatening and the only cure is liver transplant.

### type 2

- slightly more common than type 1 and less severe
- may improve with phenobarbital

# Pregnancy: jaundice

## Intrahepatic cholestasis of pregnancy (ICP):

- It is caused by a bile acid transport defect.
- It is relatively common but usually occurs in the **second** or **third** trimester (it would **not** occur in the **first** trimester).
- It is may be due to inherited susceptibility of liver cells to high oestrogen levels (a similar condition is seen in association with OCP use).
- **Itching** is the commonest symptom of ICP (often the palms and soles).
- **ALP (> 4 times)** and **GGT** is usually **high** with modest elevations in AST (< 300 IU/L) and bilirubin (< 100 Mmol/L).
- Risk increases with **multiparty**. It is more common in women with a history of cholestasis associate with **OCP** use and those who have a **family history** of ICP.
- There is an **increased risk of** foetal distress, preterm labour and perinatal death therefore careful foetal monitoring is essential.
- Long-term maternal outcome is relatively good compared to other liver conditions associated with pregnancy. **The prognosis is excellent** for the mother and the condition rapidly **resolve with 2-4 weeks after delivery** of the child. It may **recur in 40%** of cases.
- Prior to delivery, **antihistaminic**, **BDZs** and **ursodeoxycholic acid** have a role in symptom relief and sometimes **Vit K** if there is deranged clotting.

## Acute fatty liver of pregnancy (AFLP):

- It is a condition of the **third** trimester, and is common in **first** and **multiple** pregnancies.
- The diagnosis is a **clinical** one and there is characteristically an **elevated TLC**, **low glucose**, **low albumin, raised NH3 (ammonia)** level and evidence of **DIC** in up to **75%** (**prolonged INR**, **schistocytes** in blood smear).
- It is associated with abnormalities of the **synthetic** function, therefore serum **albumin** would be expected to be **low**.
- Treatment:
  - **Protein restriction ± laxative** (to ↓ ammonia load).
  - **IV dextrose** to correct hypoglycaemia,
  - **FFP** to correct coagulopathy, followed by
  - **Expeditious delivery** which results in dramatic recovery of the mother.

- The **HELLP** syndrome is associated with **preeclampsia** and there is a degree of overlap with **HUS/TTP**.

### D.D: Pregnancy with deranged LFTs:

- Hepatitis: viral A or autoimmune.
- HELLP
- Acute fatty liver of pregnancy (AFLP).
- Cholestasis of pregnancy.
- Budd-Chiari syndrome.

## Dubin-Johnson syndrome (DJS)

Dubin-Johnson syndrome is a rare **benign autosomal recessive (AR)** disorder of impaired bilirubin **excretion** resulting in mild jaundice but **normal liver function**. Resulting in **conjugated** hyperbilirubinaemia (therefore **present** in **urine**).

DJS is much less common than Gilbert's.

It is due to a **defect in the canillicular multispecific organic anion transporter (cMOAT)** protein. This causes defective hepatic bilirubin **excretion.**

**Unconjugated** bilirubin (= **indirect**): water-**insoluble**, so **not** pass to urine (normal colour).
**Conjugated** bilirubin (= **Direct**): it is **water**-soluble so **pass to urine** (**dark**).

## Budd-Chiari Syndrome

Budd-Chiari syndrome, or hepatic vein thrombosis, is usually seen in the context of underlying haematological disease or another procoagulant condition.

### Causes

- polycythaemia rubra vera
- **thrombophilia:** activated protein C resistance, antithrombin III deficiency, protein C & S deficiencies
- **pregnancy**
- **combined oral contraceptive pill:** accounts for around 20% of cases

### Features

- abdominal pain: sudden onset, severe
- ascites → abdominal distension
- **tender hepatomegaly**
- Signs of portal hypertension are present and patients may develop acute variceal haemorrhage as a complication..

**Budd-Chiari S: Triad: Abdomen pain+ tender Hepatomegaly + Ascites**

The chronic form presents more insidiously with signs of cirrhosis and portal hypertension.

**Three**-year survival in patients with chronic Budd-Chiari syndrome is **50%.**

## Investigations:

- **Colour Doppler US for hepatic vasculature.**
- US, CT or MRI Abdomen: **enlarged caudate lobe: is a characteristic sign** but is seen in **only 50%** of cases.
- Ascitic tap usually demonstrates a **high SAAG (>11g/L).**

## Management:

- Treatment of the underlying cause.
- Portocaval shunts and TIPSS
- Streptokinase and subsequent anticoagulation may be attempted if the thrombus is known to be of a recent onset.
- Liver transplantation.

**EX**: A 40-year-old woman with abdominal pain and increasing abdominal girth. Her symptoms have been progressing over several months. There is no history of jaundice. She has a **past history of pulmonary embolism** for which she was treated with warfarin 5 years ago.

O/E, she has **mildly jaundiced sclerae**. She is alert and orientated, there is no encephalopathy. Abdominal examination reveals **ascites** and **hepatosplenomegaly**.

You arrange an abdominal ultrasound scan with Dopplers which demonstrates and confirms hepatosplenomegaly and moderate ascites.

What is the most likely underlying diagnosis >>> **Budd-Chiari syndrome.**

# Autoimmune hepatitis

Autoimmune hepatitis is condition of unknown aetiology which is most commonly seen in **young females (30-50 years)**.

Recognised associations include **other autoimmune disorders** such as **ulcerative colitis**, **Hashimoto thyroiditis**, **keratoconjunctivitis sicca**, **RA** and **peripheral neuropathy**.
It is also associated with **Hypergammaglobulinaemia**.

**Diagnosis and prognostic** assessment are best informed by liver biopsy.

60% are associated with HLA-B8, DR3 and Dw3.

## Pathophysiology

T-cell mediated progressive necro-inflammatory process resulting in fibrosis and cirrhosis.

Three types of autoimmune hepatitis have been characterised according to the types of circulating antibodies present.

| Type I | Type II | Type III |
|---|---|---|
| Anti-nuclear antibodies (**ANA**) and/or anti-**smooth muscle antibodies** (**SMA**)<br>**Affects both adults and children** | Anti-liver/kidney microsomal type 1 antibodies (**LKM1**)<br>Affects **children only** | Anti-Soluble liver-kidney antigen (**SLA**)<br>**Affects adults** in middle-age |

## Features:

- **Acute hepatitis**: fever, jaundice etc. (only **25%** present in this way).
- May present with signs of **chronic liver disease:** hepatosplenomegaly, deranged liver function with a low albumin, prolonged INR and evidence of extensive hepatic necrosis.
- Features of **cirrhosis** occur in around **75%** of cases.
- The **sicca syndrome** (xerostomia, dry eyes, keratoconjunctivitis sicca) may occur.
- ANA/SMA/LKM1 antibodies.
- Raised **IgG** levels with normal IgA and IgM (although may be some ↑ IgM).
- **Liver biopsy**: the investigation of choice to **confirm** the diagnosis: inflammation extending beyond limiting plate 'piecemeal necrosis', bridging necrosis.

Autoimmune hepatitis is not usually present as an acute hepatitis (only 25%).
25% present as acute hepatitis but usually the onset is insidious.
Some may be asymptomatic for years and then are found to have signs of chronic liver disease.

## Management

- Steroids and other immunosuppressant e.g., **azathioprine** and cyclosporine (a maintenance therapy of prednisolone 10 mg + azathioprine 50 mg daily).
  - Steroid therapy does not, however, prevent progression to frank cirrhosis.
- **Liver transplantation.**

**NB:**

- The combinations of **deranged LFTs** combined with **secondary amenorrhoea** in a **young female** strongly suggest autoimmune hepatitis.
- You should think of autoimmune hepatitis after exclusion of other causes of hepatitis such as viral, alcohol and drugs.
- Smooth muscle antibodies (SMA) are associated with autoimmune hepatitis. Presentation is usually insidious and extra hepatic clinical features are common.

# Primary biliary cholangitis (Primary biliary cirrhosis)

- **Primary biliary cholangitis** is a chronic liver disorder typically seen in middle-aged **females 40-70 years** (female: male ratio of 9:1). (**90%** of cases **female**)
- The aetiology is not fully understood although it is thought to be an **autoimmune** condition.
- There is strong **association with other autoimmune conditions** (see later).
- PBC is associated with **HLA-DR3** and **HLA-DR8.**
- It is characterised by portal inflammation and immune-mediated **gradual destruction** of the **intrahepatic** bile ducts which results in reduced bile secretion and retention of toxic substances. This leads to further hepatic damage, fibrosis and **cirrhosis**.
- Interlobular bile ducts become damaged by a chronic inflammatory process causing progressive cholestasis which may eventually progress to cirrhosis.
- The classic presentation is **itching** in a **middle-aged woman**.

- PBC is characterised by **ant mitochondrial antibodies (AMA) (M2),** which are present in **90-95%** of patients (often before clinical signs develop) and have a **specificity** of **98%.**

**Positive AMA** + ↑ **ALP** + **Dyslipidaemia** >>> strongly suggestive of **BPC.**

## Associations:

- **Sjogren's** syndrome (SS) (seen in up to **80% of patients**)
- **Rheumatoid arthritis** (RA)
- Systemic sclerosis (SS) and CREST syndrome.
- **Thyroid** disease
- Membranous GN and RTA.

## Clinical features:

- Early: 50% of patients may be **asymptomatic** at diagnosis (e.g., raised **ALP** and GGT on routine LFTs) or mainly **Lethargy (fatigue), pruritus** before jaundice.
- **Lethargy** is the most common symptom **(70%)** followed by **pruritis.**
- Cholestatic **jaundice**
- **Hypercholesterolemia, Xanthelasmas,** xanthomata
- Hyperpigmentation, especially over pressure points: dermatitis herpetiformis.
- Also: clubbing, hepatosplenomegaly and portal hypertension
- Late: may progress to liver failure

Scleral icterus in a 64-year-old Hispanic woman with primary biliary cirrhosis.

In PBC, **once jaundice develop** survival is less than **2 years** and criteria for **transplantation** is **high bilirubin** > 100 Mmol/L and **intractable pruritis**.

The median survival overall **is 7-10 years**
But reduced to **less than 2 years** in the presence of **jaundice**
The 5 years survival **post-transplant** is about **70-80%.**

## Diagnosis

### Immunology

- **anti-mitochondrial antibodies (AMA) M2** subtype are present in 98% of patients and are highly specific
- smooth muscle antibodies in 30% of patients
- **raised serum IgM**

### imaging

- required before diagnosis to exclude an extrahepatic biliary obstruction (typically a right upper quadrant ultrasound or magnetic resonance cholangiopancreatography (MRCP)

## Management:

- **Ursodeoxycholic acid**: it improves liver biochemistry and delays disease progression.
- Pruritus: cholestyramine.
- Fat-soluble vitamin supplementation.
- **Liver transplantation** is the inevitable late treatment of choice especially if bilirubin > 100 (PBC is a major indication of liver TX.) –
  - **Recurrence** in graft can occur in up to 16% of cases after 5 years but is not usually a problem.

## Complications:

- **Malabsorption** of **fat-soluble vitamins** (**A**, **K**, **E**, **D**) is common: **osteomalacia**, **coagulopathy** (bruising).
- **Sicca** syndrome occurs in **80%** of cases.
- Portal hypertension: ascites, variceal haemorrhage.
- Hepatocellular cancer **(20-fold increased risk)**
- In symptomatic patients **median** survival is approximately **5 years** without transplantation.
- Overall, survival from time of diagnosis is put at between **7-17 years**.

Liver transplantation is very effective in PBC - the 5 year survival is **>80%.**

**NB**: The **two main** conditions causing pigmentation and chronic liver disease are: primary biliary cirrhosis (**PBC**) and **haemochromatosis**.

# Primary sclerosing cholangitis (PSC)

Primary sclerosing cholangitis is a **chronic cholestatic liver** disease of **unknown** aetiology characterised by inflammation and fibrosis of intra and extra-hepatic bile ducts.
Around 70% of patients diagnosed with PSC are **men**, with an average age of around 40 years.
Time from diagnosis to end-stage hepatic failure is thought to be around 12 years.
Colectomy has no the nature history of PSC development at all.

## Associations:

- **Ulcerative colitis (UC)**: **4% of patients with UC have PSC, up to 90% of patients with PSC have UC.**
- Crohn's (much less common association than UC)
- HIV

4% of patients with UC have PSC and 80% of patients with PSC have UC

## Features:

- Cholestasis:
  - jaundice and pruritus
  - raised bilirubin + ALP
- Right upper quadrant pain
- Fatigue
- Weight loss

## Investigation:

- **ERCP** is the **gold standard diagnostic tool**, showing multiple intrahepatic and extra hepatic bile duct strictures and dilatations, giving a **'beaded'** appearance.
- However, the non-invasive magnetic **MRCP** is often performed **initially**, MRCP would be **the initial diagnostic investigation of choice** particularly given a lower complication rate and its ability to image ducts proximal to obstructing strictures.
- Increase in **IgM** in 84 % of cases.
- **P-ANCA** may be positive in 65-85% of cases.
- Positive **ANA** in 55% of cases
- There is a limited role for liver biopsy, which may show fibrous, obliterative cholangitis often described as **'onion skin'**.
- Ultrasound may be normal in up to 50% of cases in early stages.

**PSC:**
The **gold standard** diagnostic tool >>> **ERCP**,
The **initial** diagnostic investigation of choice >>> **MRCP**

## Complications:

- **Cholangiocarcinoma** (in 10-15% of PSC cases)
- Increased risk of colorectal cancer

## Treatment:

- **Liver transplantation:**
  - Survival post liver transplant is around 90%, although the chance of rejection is high.
  - High dose of ursodeoxycholic acid failed to show any benefit in PSC patients.

**NB:** Most patients with severe PSC are surveyed for the possible development of cholangiocarcinoma and are recommended for **liver transplantation *before*** this occurs.

But If there is **MRI cholangiography** evidence of cholangiocarcinoma with local lymphatic invasion >>> surgical removal is likely to be unsuccessful.

The ttt of choice in this occasion is **ERCP with stenting** of the lesion, it is successful at relieving symptoms of jaundice and may also relieve associated lethargy and fatigue.

Stent replacement may be required every 3-6 months, and adjuvant radiotherapy past stent placement may prolong survival for as long as 17 months.

**EX:** Pt with **PSC** and **develop cholangiocarcinoma** with **invasion** >>> **ERCP with stenting**.

**EX:** **Male** pt. known to have **ulcerative colitis** presented with **lethargy**, **itching**, RUQ pain and a blood picture consistent with obstructive liver disease (**cholestasis**) ↑**ALP** >>> Primary sclerosing cholangitis (**PSC**) / **Cholangiocarcinoma** >>> **ERCP / MRCP**.

The most effective ttt is **liver transplantation**.

# Hereditary Haemochromatosis (HHC)

Haemochromatosis is an **autosomal recessive** disorder (AR) of iron absorption and metabolism resulting in iron accumulation.

It is caused by inheritance of **mutations in the HFE gene** on both copies of **chromosome 6**.

**Two mutations of the HFE gene** (**C282Y** and **H63D**) account for **over 90%** of cases in Europeans.

The disease is also associated with HLA-A3 and HLA-B14.

**N.B:**

- **Both** males and females are affected equally, but females are often 'protected' from the clinical features by menstrual blood loss.

**It is caused** by dysregulated iron homeostasis due to **inappropriate increased iron absorption** in the duodenum and proximal small intestine with **subsequent iron deposition in cells** of the liver, heart, pancreas and pituitary gland resulting in tissue damage and organ failure.
It is relatively common in **Caucasians**, usually presents in **men over the age** of **40 years**,

## Epidemiology

- 1 in 10 people of European descent carry a mutation in the genes affecting iron metabolism, mainly HFE
- prevalence in people of European descent = 1 in 200, making **it more common than cystic fibrosis**

The British Committee for Standards in Haematology (BCSH) published guidelines for the investigation and management of haemochromatosis.
There is continued debate about the best investigation to **screen** for haemochromatosis.

## Presenting features:

It is due to iron deposition in **(6) organs:**

**Anterior pituitary**, **skin**, **heart**, **joints**, **pancreas** (**DM**) and **liver**.

- Often asymptomatic in early disease and initial symptoms often non-specific e.g., **lethargy** and **loss of libido with erectile dysfunction**.
- **Joints: Arthralgia/arthritis often of the hands** esp. the **2nd and 3rd metacarpo-phalangeal joints (MPJ), wrist, knee** with **chondrocalcinosis** and **Pseudogout**.
- **Bronze skin pigmentation** (Skin pigmentation rather than a rash).

- **DM (MODY)**: **only 17%** of non-cirrhotic patients will have manifest diabetes at time of diagnosis.
- **Liver**: stigmata of chronic liver disease, hepatomegaly, cirrhosis, spider naevi, sparse pubic hair, hepatocellular deposition, HCC.
- **Cardiac** failure or dysrhythmia (secondary to **DCM**).
- Hypogonadism (secondary to cirrhosis and **pituitary** dysfunction- **Hypogonadotrophic hypogonadism**).

The combination of **pituitary dysfunction**, **arthralgia/arthritis**, **DM**, **hepatomegaly** (**cirrhosis**) with **normal LFTs** and **cardiomyopathy** >>>> Haemochromatosis.

Questions have previously been asked regarding which features are reversible with treatment:

| Reversible complications | Irreversible complications |
|---|---|
| • Cardiomyopathy<br>• Skin pigmentation | • Arthropathy<br>• DM<br>• Liver cirrhosis<br>• Hypogonadotrophic hypogonadism |

If cirrhosis develops, there is an increased risk of HCC.

**Transferrin saturation** is suggested as the initial screening test: a level of **more than 45%** warrants further investigation **(less than 45% usually excludes the diagnosis)**.

If the C282Y HFE mutation is not present **other genotypes** should be looked for and if present **a liver biopsy** is indicated.

In the event of rarer mutations confirmation with liver biopsy may be required.

**Ferritin** is measured to help guide further investigation and treatment:

**if more than 1000** >>> a **liver biopsy** should be performed and treatment initiated.

If the ferritin is within normal range and the liver function tests are normal patients can be followed closely.

Pt with **DM** and **impotence** with ↑ **ferritin** >>> a suspected diagnosis of haemochromatosis >>> the next most appropriate investigation is >>> **Transferrin saturation %** >>> **if elevated above 45%** >>> **genotyping** (homozygosity for **C282y HFE mutations** would next be considered and would be expected to clinch the diagnosis.

## Diagnostic tests:

- **High Transferrin saturation**.
- **Molecular genetic testing** for the **C282Y HEF** and **H63D** mutations
- Liver biopsy: Perl's stain.
- Screening for the first-degree relatives.

**BCSH guidelines suggest:**

- **General population:** transferrin saturation is considered the most useful marker. Ferritin should also be measured but is not usually abnormal in the early stages of iron accumulation
- **Testing family members:** genetic testing for HFE mutation.

These guidelines may change as HFE gene analysis become less expensive

**Screening** for haemochromatosis:

- **General population**: Transferrin saturation > ferritin
- **Family members**: HFE genetic testing

**Liver biopsy** remains the **gold standard** for the diagnosis of haemochromatosis as it quantifies iron deposition and also stages the amount of fibrosis.

## Typical iron study profile in patient with haemochromatosis:

- ↑ Iron.
- **Low** TIBC.
- ↑ Ferritin (e.g., > 500 ug/l) and
- ↑ Transferrin saturation **> 55%** in men or **> 50%** in women.

## Treatment:

- **Venesection is the first-line treatment** is the cheapest and most effective treatment The goal of therapy is to remove excess body iron stores which is commonly done via **phlebotomy**.
- Initially this is **weekly** or **twice weekly** (if tolerated) venesections of 500 $cm^3$ **until the serum ferritin is less than 50 ng/mL. Transferritin saturation should also be reduced to less than 50% if possible.**
- **Iron chelation with deferoxamine:** it is not used except in rare situations when venesection is impracticable.
- **Liver transplantation.**
- After these goals are reached maintenance therapy is typically required three to four times per year.

- When iron overload and anaemia are present concomitantly **chelation with desferrioxamine** may be required.
- Patients should be told to avoid vitamin C supplementation as this can enhance iron toxicity.
- End stage liver disease, portal hypertension and hepatocellular carcinoma (which is increased up to 200-fold) may necessitate liver transplantation.

**N.B**: Joint x-rays characteristically show **chondrocalcinosis**.

there are rare cases of families with classic features of genetic haemochromatosis but no mutation in the HFE gene

## Wilson's disease (Hepato-lenticular degeneration)

Wilson's disease is a rare **autosomal recessive** (**AR**) disorder of **copper metabolism** characterised by **failure of copper excretion in the bile** and so excessive copper deposition in the tissues especially in the **liver**, **eye** and **brain** and **impaired incorporation of copper into caeruloplasmin.**
Metabolic abnormalities include increased copper absorption from the small intestine and decreased hepatic copper excretion.
Wilson's disease is caused by a defect in the **ATP7B gene** located on **chromosome 13.**

**The average prevalence is 30/million.**
The onset of symptoms is usually **between 10 - 25 years**.
**Children** usually present with **liver** disease whereas the first sign of disease, while in **young** adults is often **neurological** disease.

Features result from excessive copper **deposition** in the **tissues**, especially the brain, liver and cornea:

- **Liver**: asymptomatic hepatomegaly, hepatitis, cirrhosis.
- **Neurological**: **Extrapyramidal** signs, **basal ganglia degeneration**, speech and behavioural problems are often the first manifestations. Also: asterixis, chorea, dementia, depression, neurotic behaviour.
- **Eye: Kayser-Fleischer (KF) rings** (copper deposition in Descemet's membrane of the cornea) by **slit-lamp examination**:
  - it is the **most rapid diagnostic pathognomonic sign** (present in **60%** of cases) (greenish gold discoloration within the limbus of cornea), although rarely it may be absent.
- **Kidney**: Renal tubular acidosis type II (esp. **Fanconi** syndrome).
- Others: **Haemolysis**, Blue nails, low serum phosphate and uric acid.

**Wilson's disease** should be suspected in **any young adult** with **neuropsychiatric symptoms** and **a family history of liver disease**.

Combination of **Parkinsonism** and **chronic liver disease** in a **young** person is highly suggestive of **Wilson's** disease.

Kayser-Fleischer ring around the cornea in a patient with Wilson disease.

## Investigations and Diagnosis:

- slit lamp examination for Kayser-Fleischer rings
- increased 24hr urinary copper excretion
- the diagnosis is confirmed by genetic analysis of the ATP7B gene
- **Reduced serum caeruloplasmin**: **< 200 mg/L: not specific.**
- Liver biopsy will aid the diagnosis.
- MRI brain commonly shows increased density in the basal ganglia.

Once a diagnosis of Wilson's disease is made, **screening** of **first**-degree relatives (with **genetic** testing) should be done.

## Management:

- **Penicillamine** (chelates copper) **(0.75-1.5 gm/day)**: it has been the traditional **first-line** treatment. It leads to urinary copper excretion.
  - side effects in ~ 30% of cases
    - (e.g., sensitivity reactions)
    - bone marrow suppression
- **Trientine HCL 50 mg TID** is an alternative chelating agent which may become first-line treatment in the future as it is less toxic.
- **Zinc 50 mg oral TID**: it inhibits intestinal absorption of copper.
- Tetrathiomolybdate is a newer agent that is currently under investigation.
- Hepatotoxic drugs, alcohol and foods high in copper (liver, chocolate, shellfish etc.) should be avoided.

# Drug-induced liver disease

Drug-induced liver disease is generally divided into hepatocellular, cholestatic or mixed. There is however considerable overlap, with some drugs causing a range of changes to the liver.

Elevation of the ALP in excess of hepatic transaminases (ALT & AST) indicates a cholestatic pattern of injury/jaundice.

## The following drugs tend to cause a hepatocellular picture:

- Paracetamol
- Sodium **valproate, phenytoin**
- MAOIs
- Halothane
- Anti-tuberculosis: isoniazid, rifampicin, pyrazinamide
- **Statins**
- Alcohol
- Amiodarone
- Methyldopa
- nitrofurantoin

## The following drugs tend to cause cholestasis (+/- hepatitis):

- **Oral contraceptive pill**
- **Antibiotics: flucloxacillin, co-amoxiclav**, ciprofloxacin, erythromycin*, nitrofurantoin
- Anabolic steroids, testosterones
- Phenothiazines: chlorpromazine, prochlorperazine
- Sulphonylureas
- Fibrates
- Rare reported causes: nifedipine

## Liver cirrhosis:

- Methotrexate
- Methyldopa
- Amiodarone

*risk may be reduced with erythromycin stearate

Flucloxacillin + co-amoxiclav are well recognised causes of cholestasis

Some drugs may produce jaundice by inducing haemolysis (for example, dapsone).

Elevation of transaminases to this extent (more than 100 times the upper limit of normal, about **10,000**) generally occurs in **only 2 conditions - ischemic hepatitis** and **paracetamol overdose**.
The near-normal INR in the presence of significant hepatocellular damage also counts against a diagnosis of paracetamol overdose.
**Halothane** induced hepatitis typically occurs **5 to 7 days after** exposure.
Statin-induced hepatitis in unlikely to have developed acutely (with normal LFTs on admission).

## Alcoholic liver disease

### Alcoholic liver disease covers a spectrum of conditions:

- alcoholic fatty liver disease
- alcoholic hepatitis
- cirrhosis

### Selected investigation findings:

- gamma-GT is characteristically elevated
- the ratio of **AST:ALT** is normally > 2, **a ratio of > 3** is strongly suggestive of acute alcoholic hepatitis

### Selected management notes for alcoholic hepatitis:

- **glucocorticoids** (e.g., prednisolone) are often used during acute episodes of alcoholic hepatitis
  - **Maddrey's discriminant function (DF)** is often used during acute episodes to determine who would benefit from glucocorticoid therapy
  - the STOPAH study compared the two common treatments for alcoholic hepatitis, pentoxyphylline and prednisolone. It showed that prednisolone improved survival at 28 days and that pentoxyphylline did not improve outcomes

**In alcoholic hepatitis:**
**DF (Discriminant Factor)** used to identify patients at high risk of mortality and to select patients for corticosteroid therapy.
DF = 4.6 X (prothrombin time- control) + Bilirubin (mg/dl).
**DF > 32** indicates a one month mortality of 50%.
**The new Glasgow Alcoholic Hepatitis Score**: based on age, serum bilirubin, BUN, Prothrombin time, peripheral blood TLC: has recently been shown to be a better scoring system in predicting mortality.
**NB**: In **alcoholic hepatitis:**
1) The **AST** is raised **more** than the ALT typically with a ratio of at least **2:1**.
**2) Macrocytosis** (high MCV).
3) Impaired **synthetic** function of liver (low albumin, elevated INR).
**4) Markedly raised IgA** and can cause mildly raised IgG and IgM.

# Non-alcoholic fatty liver disease

Non-alcoholic fatty liver disease (NAFLD) is now the most common cause of liver disease in the developed world. It is largely caused by obesity and describes a spectrum of disease ranging from:

- Steatosis - fat in the liver.
- Steatohepatitis - fat with inflammation, non-alcoholic steatohepatitis (**NASH**), see below.
- Progressive disease may cause fibrosis and liver cirrhosis.

NAFLD is thought to represent the hepatic manifestation of the **metabolic syndrome** and hence **insulin resistance** is thought to be the key mechanism leading to steatosis.

Non-alcoholic steatohepatitis (**NASH**) is a term used to describe **liver Biopsy histopathological changes similar** to those **seen in alcoholic hepatitis** in the **absence** of a history of **alcohol abuse** or consume **less** than 40 g of alcohol / week.

NASH is a **silent** liver disease and it is **almost always asymptomatic** and diagnosed **incidentally**.
The diagnosis is supported by the presence of **obesity**, **hyperglycaemia**, **hyper echogenic** hepatic parenchyma and ↑ **ALT > AST**

It is relatively common and though to affect around **3-4%** of the general population. It is more common in **men** due to the protective effects of oestrogen.
The progression of disease in patients with NASH may be responsible for a proportion of patients previously labelled as **cryptogenic cirrhosis.**

Approximately **20%** of NASH will develop **cirrhosis** and its associated complications.

## Associated factors:

- **Obesity**
- **Hyperlipidaemia**
- **Type 2 DM**
- **Jejunoileal bypass**
- **Nutritional status:** sudden weight loss may precipitate fat deposition in the liver/**starvation** or **over**-nutrition & **TPN**
- **Drugs** (e.g., amiodarone, methotrexate)
- Metabolic abnormalities (e.g. galactosemia, glycogen storage diseases).

## Features:

- Usually, asymptomatic
- Hepatomegaly
- **ALT** is typically greater than AST
- Increased **echogenicity** on ultrasound
- By far the most likely diagnosis in an obese type 2 DM is non-alcoholic fatty liver disease. This patient will require a liver screen, ultrasound and **liver biopsy** to confirm the diagnosis.
- A normal **ferritin** makes a diagnosis of **haemochromatosis** unlikely, although **it should always be considered in patients with both abnormal LFTs and diabetes.**

An excellent review by Byrne et al, in 2018 reviewed the diagnosis and monitoring of NAFLD. Please refer to for further details.

## Management:

- The mainstay of treatment is **lifestyle changes** (particularly **weight loss**, low fat and low calories diet) and monitoring: **supervised exercise program with group weight loss counselling.**

**Tips Obese T2DM with abnormal LFTs –think of --- non-alcoholic fatty liver disease**

## Advanced level

- **In secondary or tertiary care settings only, consider pioglitazone or vitamin E for adults with advanced liver fibrosis, whether they have diabetes or not.**
- **Before prescribing pioglitazone or vitamin E to adults, take into account any comorbidities that they have and the risk of adverse events associated with these conditions.**
- **Ursodeoxycholic acid with vit. E have shown some benefits.**
- **Pentoxyphyllin is effective but limited use by side effects(nausea).**
- **Offer to retest people with advanced liver fibrosis 2 years after they start a new pharmacological therapy to assess whether treatment is effective.**

**Weight loss** of **1 kg/week** with an initial target **loss of 10% body weight** has been shown to be effective at restoring normal liver function.

## Alcohol induced hypoglycemia

- Alcohol metabolized to acetyl-CoA.
- **NADH produced during alcohol metabolism interferes with gluconeogenesis.**
- NADH causes production of: lactate, malate, and glycerol 3-phosphate.
- Thus, glycerol 3-phosphate causes **lipid accumulation in liver alcoholic disease.**
- **NAD, required for lactate metabolism (and lactate is used for gluconeogenesis), is being used for alcohol metabolism.**

**The large anion gap and hypoglycemia in alcoholic patients can be explained by which mechanism?**

- **Inhibition of dehydrogenase enzymes by NADH**
  - Excess alcohol intake leads to accumulation of NADH that **decreases gluconeogenesis** as well as impairs fatty acid oxidation.
  - ( Key gluconeogenic dehydrogenases are inhibited by the elevated levels of NADH, including:
    - lactate dehydrogenase,
    - glycerol 3-phosphate dehydrogenase, and
    - malate dehydrogenase).

## liver abscess

### Amoebic liver abscess

C/O: Fever, RUQ abdominal pain with tenderness hepatomegaly and weight loss in **endemic tropical** countries. It can be **indistinguishable** from pyogenic abscess.

It can often present **without bowel changes** in up to **50%** of cases.

**Serum anti Entamoeba histolytica antibody** can be found in over **95%** of cases, but this could be **past** or **present** infection.

**Stool antigen detection** may be helpful and facilitates early diagnosis before an antibody response occurs (< 7 days) and differentiates pathogenic from non-pathogenic Entamoeba infection.

### Treatment:

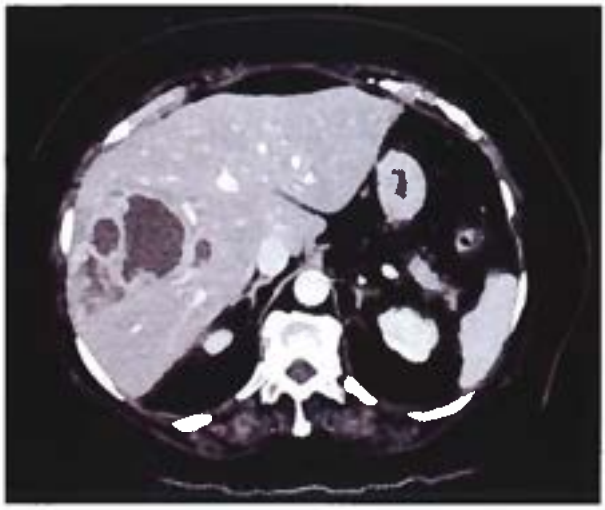
- **10-day course of metronidazole.**
- For larger liver abscesses aspiration is the intervention of choice, combined with antibiotic therapy.

## Pyogenic liver abscess

The most common organisms found in pyogenic liver abscesses are Staphylococcus aureus in children and Escherichia coli in adults.

### Treatment:

- **drainage (typically percutaneous) and antibiotics**
- **Ideally, a penicillin-based β-lactamase antibiotic combined with metronidazole to provide anaerobic cover would be the treatment of choice.**
- amoxicillin + ciprofloxacin + metronidazole
- if penicillin allergic: ciprofloxacin + clindamycin



CT showing a pyogenic liver abscess in the right lobe of the liver.

## Hydatid cysts

It is uncommon in Europe and USA but common in **Middle East** and **South America** and in **sheep**-rearing areas such as **Australia, China, Japan and Russia**, caused by the tapeworm parasite **Echinococcus granulosus.** An outer fibrous capsule is formed containing multiple small daughter cysts. These cysts are allergens which precipitate a **type 1 hypersensitivity reaction**.

Hydatid cyst is often **asymptomatic**, but can present with hepatomegaly, obstructive jaundice, fever and cholangitis.

U.S and CT: Liver is the most common site.

**Serology is neither sensitive nor specific.**

### Treatment:

- **High dose oral Albendazole** 10 mg/kg for 1-3 months followed by **percutaneous aspiration** of the cysts and **sterilisation** with alcohol or hypertonic saline.

## Hepatocellular carcinoma (HCC)

HCC is the third most common cause of cancer worldwide.

- **Chronic hepatitis B is the most common cause of HCC worldwide**
- **While, chronic hepatitis C being the most common cause in Europe.**

The main risk factor for developing HCC is liver cirrhosis, for example secondary to hepatitis B & C, alcohol, haemochromatosis and primary biliary cirrhosis.

### Other risk factors include:

- Alpha-1 antitrypsin deficiency
- Hereditary tyrosinosis
- Glycogen storage disease
- Aflatoxin
- Drugs: oral contraceptive pill, anabolic steroids
- Porphyria cutanea tarda
- **Male** sex
- **DM**, metabolic syndrome
  *Wilson's disease is an exception

### Features:

- Tends to present late
- Features of liver cirrhosis or failure may be seen: jaundice, ascites, RUQ pain, hepatomegaly, pruritus, splenomegaly
- Possible presentation is decompensation in a patient with chronic liver disease
- raised AFP

**Screening** with ultrasound (+/- alpha-fetoprotein) should be considered for high risk groups such as:

- Patients with liver cirrhosis secondary to hepatitis B & C or haemochromatosis.
- **Men** with liver **cirrhosis** secondary to **alcohol.**

## Management options:

The only proven potentially curative therapy for HCC remains **surgical, either hepatic resection or liver transplantation.**

- **Hepatic resection** should be considered as a primary therapy in any patient with HCC and **non-cirrhotic** liver.
- **Liver transplantation** should be in any patient with **cirrhosis** and a **single small HCC < 5 cm** or **multiple up to 3 lesions < 3 cm**.
- Non-surgical therapy is **only** used when **surgical therapy is not** possible and with **extra hepatic dissemination**.
- **Percutaneous ethanol injection** has been shown to produce necrosis of **small** HCC and is best used in **peripheral** lesions.
- **TACE** can produce tumour necrosis and has been shown to affect survival in highly selected patients with good liver reserve.
- **Radiofrequency ablation (RF).**
- Systemic chemotherapy has a poor response rate.
- Hormonal therapy like tamoxifen has no survival benefit in controlled trials.
- **Sorafenib**: a multikinase inhibitor.
- Interferon has been used as ttt of HCC rather than the underlying viral infection, but remains controversial.

# Liver transplant

Criteria for liver transplant in fulminant failure in cases of paracetamol overdose include:

- **Arterial pH lower than 7.3** or All of the following:
  - Prothrombin time greater than 100 seconds
  - Creatinine greater than 300 µmol/L, and
  - Grade 3-4 encephalopathy
- Criteria for liver transplant in fulminant failure in non-paracetamol cases include:
  - INR greater than 6.7 or
  - prothrombin time greater than 100 seconds
- **Any three of the following:**
  - Age less than 10 years or more than 40 years
  - Jaundice more than seven days before encephalopathy
  - INR greater than 4 or prothrombin time greater than 50 seconds, and Bilirubin greater than 300 µmol/L.

# Liver biopsy

## Contraindications to percutaneous liver biopsy:

- Deranged clotting (e.g. **INR > 1.4)**
- Low platelets (e.g. **< 60 X 109/l)**
- Anaemia
- Bile duct **obstruction / dilatation**
- Hydatid cyst
- Haemoangioma
- Ascites
- Uncooperative patient: as sudden movement can result in laceration to the liver.

Anti-platelet medication should be stopped for at least 7days prior to biopsy.

If the INR is >1.4, fresh frozen plasma (FFP) may be administered and liver biopsy then carried out if the INR is less than 1.4.

Significant volume ascites is a contraindication to percutaneous liver biopsy but a transjugular biopsy can be performed as an alternative.

**NB**: With modern techniques such as ERCP and MRCP the risks of liver biopsy when there is extra-hepatic biliary obstruction are rarely justified.

# Biliary Tract

## Ascending cholangitis

Ascending cholangitis is a bacterial infection (typically *E. coli*) of the biliary tree. The most common predisposing factor is gallstones.

**Charcot's triad** of right upper quadrant (RUQ) pain, fever and jaundice occurs in about 20-50% of patients

- **fever is the most common feature, seen in 90% of patients**
- RUQ pain 70%
- jaundice 60%
- hypotension and confusion are also common (the additional 2 factors in addition to the 3 above make Reynolds' pentad)

### Other features:

- raised inflammatory markers

### Investigation:

- **ultrasound** is generally used first-line in suspected cases to look for bile duct dilation and bile duct stones

### Management:

- intravenous antibiotics
- endoscopic retrograde cholangiopancreatography (ERCP) after 24-48 hours to relieve any obstruction

## Bile-acid malabsorption

**Bile-acid malabsorption as a cause of chronic diarrhea.**
This may be primary, due to excessive production of bile acid, or secondary to an underlying gastrointestinal disorder causing reduced bile acid absorption.
**It can lead to steatorrhea and vitamin A, D, E, K malabsorption.**
Secondary causes are often seen in patients with ileal disease, such as with Crohn's. Other secondary causes include:

- cholecystectomy
- coeliac disease
- small intestinal bacterial overgrowth
- overdose of metformin(more than 2000 mg /day) for longer than 2 years.

## Investigation

- **the test of choice is SeHCAT**
- nuclear medicine test using a gamma-emitting selenium molecule in selenium homocholic acid taurine or tauroselcholic acid (SeHCAT)
- scans are done 7 days apart to assess the retention/loss of radiolabelled $^{75}$SeHCAT

## Management

- **bile acid sequestrants e.g., cholestyramine**

# Nutrition in Gastroenterology

## Malnutrition

Malnutrition is an important consequence of and contributor to chronic disease.
It is clearly a complex and multifactorial problem that can be difficult to manage but there are a number of key points to remember for the exam.

**NICE define malnutrition as the following:**

- a Body Mass Index (BMI) of less than 18.5; or
- unintentional weight loss greater than 10% within the last 3-6 months; or
- a BMI of less than 20 and unintentional weight loss greater than 5% within the last 3-6 months

Around 10% of patients aged over 65 years are malnourished, the vast majority of those living independently, i.e. not in hospital or care/nursing homes.

**Screening for malnutrition** if mostly done using MUST (Malnutrition Universal Screen Tool). A link is provided to a copy of the MUST score algorithm.

- it should be done on admission to care/nursing homes and hospital, or if there is concern. For example an elderly, thin patient with pressure sores
- it takes into account BMI, recent weight change and the presence of acute disease
- categorises patients into low, medium and high risk

**Management** of malnutrition is difficult. NICE recommend the following points:

- dietician support if the patient is high-risk
- a 'food-first' approach with clear instructions (e.g. 'add full-fat cream to mashed potato'), rather than just prescribing oral nutritional supplements (ONS) such as Ensure
- if ONS are used they should be taken between meals, rather than instead of meals

# Protein losing enteropathy

## Definition

- excessive leakage of plasma proteins into the lumen of the GIT
- refers to any condition of the GIT that results in a net loss of protein from the body.

## Causes

**lymphatic obstruction, (lymphatic leakage secondary to obstruction.): e.g:**

- primary intestinal lymphangiectasia,
- conditions associated with venous stasis such as right-sided heart failure.

**mucosal disease:**

- inflammatory exudation through mucosal damage:
  - inflammatory bowel diseases,
  - NSAID enteropathy,
  - GI malignancy.
- increased permeability from non-erosive mucosal disease
  - amyloidosis,
  - GI infections,
  - rheumatic diseases,

## Features

- The most common presenting symptom is **swelling of the legs** due to decreased plasma **oncotic** pressure.
  - bilateral oedema from hypoproteinaemia is generalised and may be seen in the peri-orbital region as well as in the extremities
- diarrhoea

## Investigations

- **Measurement of α1-Antitrypsin in a sample of faeces**
  - **the most appropriate to confirm the diagnosis**
  - Albumin is degraded by proteases in the gut; however, α1-antitrypsin is a plasma protein that is resistant to degradation by proteases (it is a protease inhibitor) and its measurement can indicate leakage of plasma proteins into the gut.
- Serum albumin
  - albumin level <20 g/L (<2 g/dL) is usually required to cause peripheral oedema

- Finding of low serum albumin prompts investigation to determine whether the aetiology is due to loss in the urine, hepatic synthetic dysfunction, or gastrointestinal losses. History of significant diarrhoea in conjunction with ruling out alternative causes makes the diagnosis.

**Treatment:** Treat the underlying disease.

## Total parenteral nutrition

### Basics

- Commonly used in nutritionally compromised surgical patients
- Bags contain combinations of glucose, lipids and essential electrolytes, the exact composition is determined by the patients nutritional requirements.
- Although it may be infused peripherally, this may result in thrombophlebitis.
- Longer term infusions should be administered into a central vein (preferably via a PICC line).
- Complications are related to sepsis, re-feeding syndromes and hepatic dysfunction.

## Enteral feeding

### Definition

- Enteral feeding = any route of feeding that utilizes the patient's GI tract to deliver appropriate nutrition (differs from parenteral nutrition, which delivers nutrition intravenously, completely bypassing the GI tract)

### Enteral nutrition VS parenteral nutrition

- Enteral nutrition is preferred to parenteral nutrition whenever feasible - if the GI tract is functional, use it - benefits include improved absorption, immunological benefits, and helps maintain a healthy and functional GI tract

### Routes of enteral feeding:

**Short-term: nasogastric tubes**

- Consider gastric feeding unless upper GI dysfunction (then for duodenal or jejunal tube)

**Long-term** (> 2–3 weeks): gastrostomy or jejunostomy tubes

- Gastric feeding > 4 weeks consider long-term gastrostomy

**gastrostomy tube:**

- mainly used in cases of proximal gastrointestinal tract obstruction to facilitate feeding.
- **If it withdrew accidentally,** reinsertion of the tube as soon as possible would be the preferred action. However, it needs a good level of expertise to do this.
    - Therefore, in this case, **insertion of a Foley's catheter is the best practice** as it is easy to do, and this should preserve the opening of the skin and anterior abdominal wall muscles until a someone experience enough is available to re-insert the gastrostomy tube.

## How to check NG placement?

**Check NG placement using aspiration and pH (check post pyloric tubes with AXR)**

- **The first line investigation to confirm correct placement of a nasogastric tube is >> pH testing of gastric aspirate using indicator paper**
    - If the pH is between 1 and 5.5 then this is confirmatory evidence of correct placement.
    - If the pH reading is between 5.5 and 6 it is recommended that a second independent reading is made to confirm.
    - if aspirate pH ≥6 >> nasogastric feeding tubes feeding cannot be commenced
- If there is any doubt, then an appropriately interpreted **chest x ray is a second line investigation.**

**Key points**

- **Identify** patients as malnourished or at risk (see below)
- Identify unsafe or inadequate oral intake with functional GI tract
- Consider bolus or continuous feeding into the stomach
- PEG can be used 4 hours after insertion but should not be removed until >2 weeks after insertion.

**Indications**

**pre-operative**

- Surgical patients due to have major abdominal surgery: if malnourished, unsafe swallow/inadequate oral intake and functional GI tract then consider pre-operative enteral feeding.

**ITU patients**

- ITU patients should have continuous feeding for 16-24h (24h if on insulin)

- Consider motility agent in ITU or acute patients for delayed gastric emptying. If this doesn't work, then try post pyloric feeding or parenteral feeding.

**Contraindications**

- Mechanical ileus, bowel obstruction
- Acute abdomen (e.g., severe pancreatitis, peritonitis)
- Upper GI bleeding
- Mucositis
- Severe substrate malabsorption
- Congenital GI anomalies
- High-output fistulas
- Nonfunctional GI tract (e.g., gastroschisis, short bowel syndromes)

**Causes of diarrhoea in patients receiving enteral nutrition:**

- hyperosmolar feed
- bacterial contamination
- low feed temperature
- reduced intestinal absorptive capacity
- too rapid or irregular administration
- lactose intolerance.

**Causes of constipation in patients receiving enteral nutrition:**

- **Inadequate fluid replacement**

## Refeeding syndrome

Refeeding syndrome describes the metabolic abnormalities which occur on feeding a person following a period of starvation.
It occurs when an extended period of catabolism ends abruptly with switching to carbohydrate metabolism.

**The metabolic consequences include:**

- **hypophosphataemia**
- hypokalaemia
- hypomagnesaemia: may predispose to **torsades de pointes**
- abnormal fluid balance

**These abnormalities can lead to organ failure.**

### Pathophysiology:

- When malnourished, the body uses endogenous fuel stores for energy and maintains serum electrolytes by redistribution from intracellular spaces.

- **Exogenously administered glucose results in insulin release. This results in rapid uptake of glucose, potassium, phosphate and magnesium into cells, with dramatic falls in the extracellular concentrations.**

## Prevention

NICE produced guidelines in 2006 on nutritional support. Refeeding syndrome may avoided by identifying patients at a high-risk of developing refeeding syndrome:

Patients are considered **high-risk if one or more of the following**:

- BMI < 16 kg/m$^2$
- unintentional weight loss >15% over 3-6 months
- little nutritional intake > 10 days
- hypokalaemia, hypophosphataemia or hypomagnesaemia prior to feeding (unless high)

**If two or more of the following:**

- BMI < 18.5 kg/m$^2$
- unintentional weight loss > 10% over 3-6 months
- little nutritional intake > 5 days
- history of: alcohol abuse, drug therapy including insulin, chemotherapy, diuretics and antacids

**NICE recommend that if a patient hasn't eaten for > 5 days, aim to re-feed at no more than 50% of requirements for the first 2 days.**

## Management

- Correcting electrolyte abnormalities aggressively

it may be preferable to provide electrolyte replenishment prior to commencing calorific intake

A patient with a history of **alcoholism** is admitted for **re-feeding**. Which component of the feed may need to be reduced **to avoid encephalopathy**?

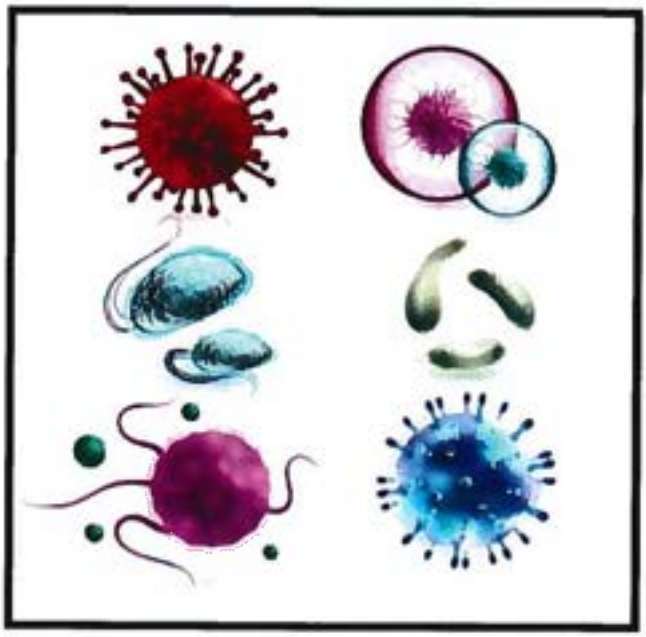
- **Protein**
  - protein content of feeds should be strictly managed in patients with alcoholism.
  - Protein rich feeds >> ↑ total ammonia burden >> **↑ risk of encephalopathy**.

## Miscellaneous

For assessment of **nutritional status** >>> **Mid-arm muscle circumference** and **skin-fold thickness**.

**Radiation enteritis**: radiation injury to the rectum and sigmoid colon is commonly seen following ttt of cancers of the cervix, uterus, prostate and bladder. It often occurs 9 to 14 months following radiation exposure and results in chronically ischaemic intestinal segment that may lead to stricture.

# Infectious Diseases & STDs



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# Basics of Infectious Diseases

## Basics of Infectious Diseases

### Classification of bacteria

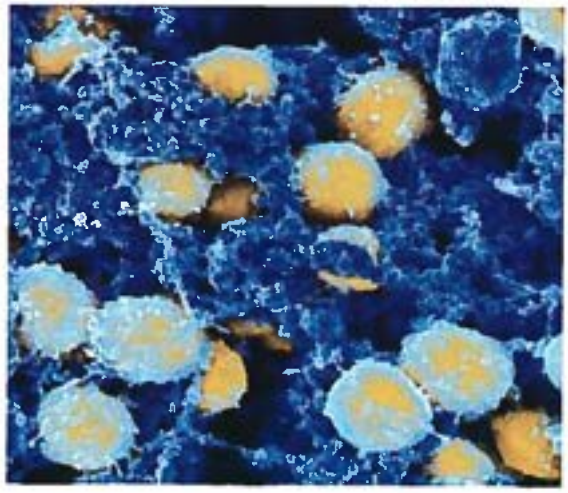
- **Gram Positive cocci** = staphylococci + streptococci (including enterococci).
- **Gram Negative cocci** = Neisseria meningitidis + Neisseria gonorrhoeae, also Moraxella.

Therefore, only a small list of Gram-positive **rods** (bacilli) needs to be memorised - mnemonic = **ABCD L.**

- **A**ctinomyces.
- **B**acillus anthracis (anthrax).
- **C**lostridium.
- **D**iphtheria: Corynebacterium diphtheriae.
- **L**isteria monocytogenes.

Remaining organisms are **Gram negative rods.**

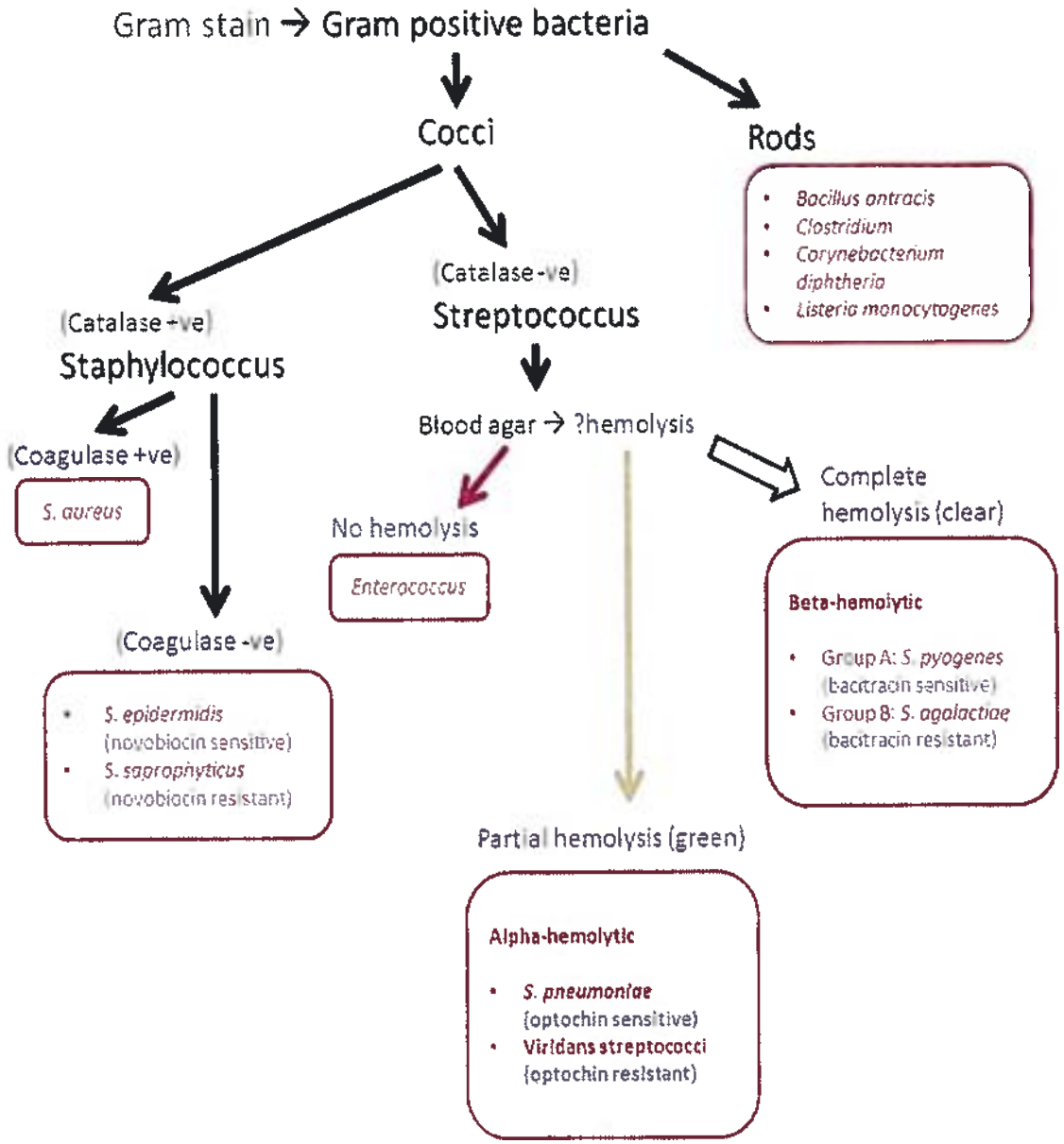
- Escherichia coli
- Haemophilus influenzae
- Pseudomonas aeruginosa
- Salmonella sp.
- Shigella sp.
- Campylobacter jejuni



Scanning electromicrograph of Staphylococcus aureus bacteria. Credit: NIAID

# Identifying gram-positive bacteria

Gram-positive bacteria will turn purple/blue following the gram staining. Microscopy will then reveal the shape, either cocci or rods.



### Rods (bacilli)

- Actinomyces
- Bacillus antracis
- Clostridium
- Corynebacterium diphtheriae
- Listeria monocytogenes

### Cocci

- makes catalase: **Staphylococci**
- does not make catalase: Streptococci

### Staphylococci

- makes coagulase: **S. aureus**
- does not make coagulase: *S. epidermidis* (novobiocin sensitive), *S. saprophyticus* (novobiocin resistant)

### Streptococci

- partial haemolysis (green colour on blood agar): **α-haemolytic**
- complete haemolysis (clear): **β-haemolytic**
- no haemolysis: γ-haemolytic

### α-haemolytic streptococci

- optochin sensitive: *S. pneumoniae*
- optochin resistant: Viridans streptococci

### β-haemolytic streptococci

- bacitracin sensitive: Group A: *S. pyogenes*
- bacitracin resistant: Group B: *S. agalactiae*

## Exotoxins and endotoxins

Exotoxins are secreted by bacteria whereas endotoxins are only released following lysis of the cell.
Exotoxins are generally released by Gram positive bacteria with the notable exceptions of *Vibrio cholerae* and some strains of *E. coli*

**It is possible to classify exotoxins by their primary effects:**

- pyrogenic toxins
- enterotoxins
- neurotoxins
- tissue invasive toxins
- miscellaneous toxins

## Pyrogenic toxins

Pyrogenic toxins stimulate the release of endogenous cytokines resulting in fever, rash etc.

They are superantigens which bridge the MHC class II protein on antigen-presenting cells with the T cell receptor on the surface of T cells resulting in massive cytokine release.

| Organism | Toxin | Notes |
|---|---|---|
| Staphylococcus aureus | Toxic shock syndrome (TSST-1 superantigen) toxin | Results in high fever, hypotension, exfoliative rash |
| Streptococcus pyogenes | Streptococcal pyrogenic exotoxin A & C | Results in scarlet fever |

## Enterotoxins

Enterotoxins act on the gastrointestinal tract causing one of two patterns of illness:

- diarrheal illness
- vomiting illness ('food poisoning')

| Organism | Toxin | Notes |
|---|---|---|
| Vibrio cholerae | Cholera toxin | Causes activation of adenylate cyclase (via $G_s$) leading to increases in cAMP levels, which in turn leads to increased chloride secretion and reduced sodium absorption |
| Shigella dysenteriae | Shiga toxin | Inactivates 60S ribosome → epithelial cell death |
| Escherichia coli | 1. Heat labile toxin<br>2. Heat stabile toxin | 1. Activates adenylate cyclase (via $G_s$), increasing cAMP → watery diarrhoea<br>2. Activates guanylate cyclase, increasing cGMP → watery diarrhoea |
| Staphylococcus aureus | Staphylococcus aureus enterotoxin | Vomiting and diarrhoeal illness lasting < 24 hours |
| Bacillus cereus | Cereulide | Potent cytotoxin that destroys mitochondria. Causes a vomiting illness which may present within 4 hours of ingestion |

## Neurotoxins

Neurotoxins act on the nerves (tetanus) or the neuromuscular junction (botulism) causing paralysis.

| Organism | Toxin | Notes |
|---|---|---|
| Clostridium tetani | Tetanospasmin | Blocks the release of the inhibitory neurotransmitters GABA and glycine resulting in continuous motor neuron activity → continuous muscle contraction → lockjaw and respiratory paralysis |
| Clostridium botulinum | Botulinum toxin | Blocks acetylcholine (ACh) release leading to flaccid paralysis |

## Tissue invasive toxins

| Organism | Toxin | Notes |
|---|---|---|
| Clostridium perfringens | α-toxin, a lecithinase | Causes gas gangrene (myonecrosis) and haemolysis |
| Staphylococcus aureus | Exfoliatin | Staphylococcal scalded skin syndrome |

## Miscellaneous toxins

| Organism | Toxin | Notes |
|---|---|---|
| Corynebacterium diphtheriae | Diphtheria toxin | ADP ribosylates elogation factor (EF-2), resulting in inhibition, causing a 'diphtheric membrane' on tonsils caused by necrotic mucosal cells. Systemic distribution may produce necrosis of myocardial, neural and renal tissue |
| Pseudomonas aeruginosa | Exotoxin A | Also inhibits EF-2 by the same mechanism as above |
| Bacillus anthracis | Oedema factor (EF) | Forms a calmodulin-dependent adenylate cyclase which increases cAMP, impairing the function of neutrophils/macrophages → reduced phagocytosis |
| Bordetella pertussis | Pertussis exotoxin | Inhibits $G_i$ leading to increases in cAMP levels, impairing the function of neutrophils/macrophages → reduced phagocytosis |

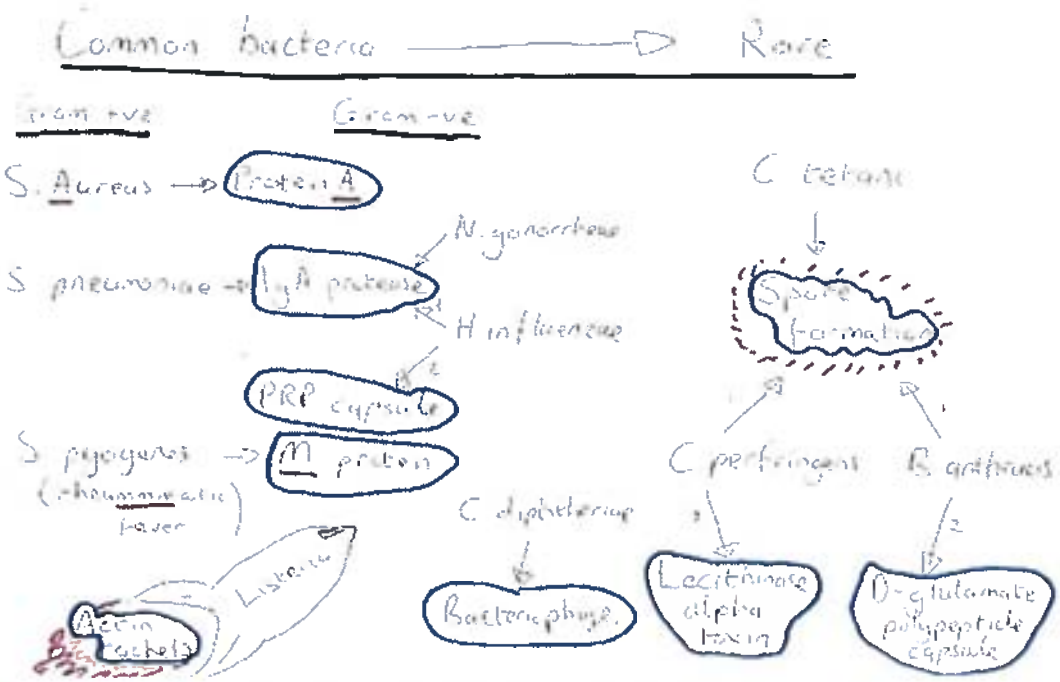
## Endotoxins

Endotoxins are lipopolysaccharides that are released from Gram-negative bacteria such as Neisseria meningitidis.

# Virulence factors

Bacteria employ a large number of virulence factors which enable them to colonize the host and evade/suppress the immune response.
The table below shows a select number of virulence factors which are important for the exam.

| Virulence factor | Example organisms |
|---|---|
| IgA protease | Streptococcus pneumoniae<br>Haemophilus influenzae<br>Neisseria gonorrhoeae |
| M Protein | Streptococcus pyogenes |
| Polyribosyl ribitol phosphate capsule | Haemophilus influenzae |
| Bacteriophage | Corynebacterium diphtheriae |
| Spore formation | Bacillus anthracis<br>Clostridium perfringens<br>Clostridium tetani |
| Lecithinase alpha toxin | Clostridium perfringens |
| D-glutamate polypeptide capsule | Bacillus anthracis |
| **Actin rockets** | Listeria monocytogenes |



# Antibiotics

## Antibiotics: mechanisms of action

The lists below summarise the site of action of the commonly used antibiotics

### Inhibit cell wall formation (beta-lactams)

- penicillins: binds transpeptidase blocking cross-linking of peptidoglycan cell walls
- cephalosporins

### Inhibit protein synthesis: these antibiotics are bateriostatic

- aminoglycosides (cause misreading of mRNA)
- chloramphenicol
- macrolides (e.g. erythromycin)
- tetracyclines
- fusidic acid

### Inhibit DNA synthesis

- quinolones (e.g. ciprofloxacin)
- metronidazole
- sulphonamides
- trimethoprim

### Inhibit RNA synthesis

- rifampicin

## Antibiotics: bactericidal vs. bacteriostatic activity

| Bactericidal | Bacteriostatic |
|---|---|
| ➢ Penicillins | ➢ Macrolides |
| ➢ Cephalosporins | ➢ Chloramphenicol |
| ➢ Isoniazid | ➢ Tetracyclines |
| ➢ Aminoglycosides | ➢ Sulphonamides |
| ➢ Quinolones | ➢ Trimethoprim |
| ➢ Rifampicin | ➢ Linezolid |
| ➢ Nitrofurantoin | ➢ Dalacin |
| ➢ Metronidazole | ➢ Doxycycline |
| | ➢ Quinu-pristin & Dalfo-pristin |

## Linezolid

It is a type of oxazolidonone antibiotic & has been introduced in recent years.

It **inhibits bacterial protein synthesis** by stopping formation of the **70s** initiation complex and is **bacteriostatic** nature.

**Spectrum**, highly active against Gram positive organisms including:

- **MRSA** (Methicillin-resistant *Staphylococcus aureus*)
- **VRE** (Vancomycin-resistant enterococcus)
- **GISA** (Glycopeptide Intermediate *Staphylococcus aureus*)

### Adverse effects:

- **Thrombocytopenia** (**reversible** on stopping).
- Monoamine oxidase MAO inhibitor: avoid tyramine containing foods.

## Macrolides

Erythromycin was the first macrolide used clinically.

Newer examples include clarithromycin and azithromycin.

Macrolides act by **inhibiting bacterial protein synthesis**. If pushed to give an answer they are **bacteriostatic** in nature, but in reality this depends on the dose and type of organism being treated.

### Adverse effects:

- GIT: Nausea is less common with clarithromycin than erythromycin.
- Cholestatic jaundice: risk may be ↓if erythromycin stearate is used.
- P450 inhibitor (see below).

### Common interactions:

**Statins should be stopped whilst taking a course of macrolides.**

Macrolides inhibit the cytochrome P450 isoenzyme CYP3A4 that metabolises statins. Taking macrolides concurrently with statins significantly increases the risk of statin-induced myopathy and rhabdomyolysis.

**NB**: Statins + Erythromycin/Clarithromycin > an important and common interaction
**NB: Erythromycin** is used in **Gastroparesis** as it has **prokinetic properties** It **Promotes gastric emptying.**

## Quinolones

Quinolones are a group of antibiotics which work by **inhibiting DNA synthesis** and are **bactericidal** in nature. Examples include: Ciprofloxacin and Levofloxacin.

### Mechanism of action:

- **Inhibit** topoisomerase II (**DNA gyrase**) and topoisomerase IV.

### Adverse effects:

- **Lower seizure threshold** in patients with epilepsy.
- **Tendon damage** (including **rupture**) - the risk is increased in patients also taking steroids.
- **Cartilage damage** has been demonstrated in animal models and for this reason quinolones are generally avoided (but not necessarily contraindicated) in children.

Ciprofloxacin >>> **Tendinopathy**, e.g. rupture tendo-achilis

This patient has Tendon damage is a well-documented complication of quinolone therapy. It appears to be an **idiosyncratic** reaction, with the actual median duration of treatment being 8 days before problems occur.

The classical signs of **Achilles tendon** rupture is a sudden, acute onset of pain at the back of the ankle whilst jogging, during which a heard cracking sound.

The BNF advises that **quinolones** 'should be used with **caution** in patients with a history of **epilepsy**, or **conditions that predispose to seizures**'

## Tetracyclines

Tetracyclines are a class of antibiotics which are commonly used in clinical practice.

### Examples

- doxycycline
- tetracycline

### Mechanism of action

- protein synthesis inhibitors
- binds to 30S subunit blocking binding of aminoacyl-tRNA

### Mechanism of resistance

- increased efflux of the bacteria by plasmid-encoded transport pumps, ribosomal protection

### Indications

- acne vulgaris
- Lyme disease
- Chlamydia
- Mycoplasma pneumoniae

### Notable adverse effects

- discolouration of teeth: therefore should not be used in children < 12 years of age
- **photosensitivity**
- angioedema
- black hairy tongue

Tetracyclines should not be given to women who are pregnant or breastfeeding due to the risk of discolouration of the infant's teeth.

## Quinupristin & Dalfopristin antibiotics

### Overview:

- Injectable streptogrammin antibiotic.
- Combination of group A and group B streptogrammin.
- **Inhibits bacterial protein synthesis** by blocking t-RNA complexes binding to the ribosome.

### Spectrum:

- **Most Gram-positive bacteria**
- **Exception: Enterococcus faecalis** (not to be confused with Enterococcus faecium, which is sensitive to Quinupristin & dalfopristin).

### Adverse effects:

- **Thrombophlebitis** (so should give via a **central line**)
- **P450 inhibitor**
- Arthralgia

## Sulfonamides

Antibacterial sulfonamides act as competitive inhibitors of the enzyme DHPS (Di hydro pteroate synthetase), an enzyme involved in folate synthesis.

### Other uses:

**The sulfonamide chemical moiety is also present in other medications that are not antimicrobials such as:**

- Loop diuretics: Furosemide, Bumetanide, and Torsemide.
- Thiazide diuretics: Hydrochlorothiazide, Indapamide, Metalazone.
- Sulfonylureas.
- CO X 2 inhibitors: Celecoxib.
- Acetazolamide.
- Sulfasalazine.

**Co-trimoxazole**: Sulfonamide antibiotic combination of trimethoprim & sulphamethoxazole (**TMP+SMT**) in the ratio of **(1:5)**. that is used in the management of *Pneumocystis jiroveci* pneumonia

**Antibiotic sulfonamides:**

- Sulfamethoxazole
- sulfadiazine
- sulfisoxazole

**Adverse effects of co-trimoxazole include:**

- hyperkalaemia
- headache
- rash (including Steven-Johnson Syndrome)

## Vancomycin

Vancomycin is a glycopeptide antibiotic used in the treatment of Gram-positive infections, particularly methicillin-resistant *Staphylococcus aureus* (MRSA).

### Mechanism of action

- inhibits cell wall formation by binding to D-Ala-D-Ala moieties, preventing polymerization of peptidoglycans

### Mechanism of resistance

- alteration to the terminal amino acid residues of the NAM/NAG-peptide subunits (normally D-alanyl-D-alanine) to which the antibiotic binds

### Adverse effects

- nephrotoxicity
- ototoxicity
- thrombophlebitis
- red man syndrome; occurs on rapid infusion of vancomycin

## Trimethoprim

**Mechanism of action** of **trimethoprim** >> interferes with DNA synthesis by inhibiting dihydrofolate reductase.

- may, therefore, **interact with methotrexate**, which also inhibits dihydrofolate reductase

### Adverse effects:

- **Myelosuppression**
- **Transient rise in creatinine**: trimethoprim **competitively inhibits the tubular secretion of creatinine** resulting in a temporary increase which reverses upon stopping the drug
  - trimethoprim, causing a hyperkalaemic distal RTA (type 4). It also inhibits creatinine secretion, often leading to an increase in creatinine by around 40 points (but not necessarily causing AKI)

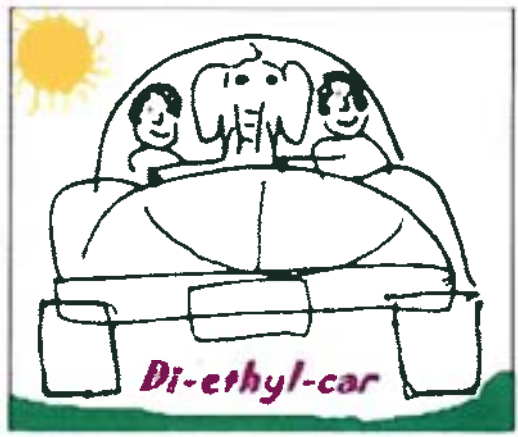
### Use in pregnancy

- the BNF advises that there is a: 'Teratogenic risk in first trimester (folate antagonist). Manufacturers advise avoid during pregnancy.'

## Diethylcarbamazine

There are two **(Di)** women named **Ethyl** in this **car**: **Di-ethyl-car**. You will notice that there is an elephant between Ethyl and Ethyl.

Used in Treatment of **filariasis** (ELEPHANTiasis)



## Metronidazole

Metronidazole is a type of antibiotic that works by forming reactive cytotoxic metabolites inside the bacteria.

### Adverse effects

- disulfiram-like reaction with **alcohol**
- increases the anticoagulant effect of warfarin

## Antibiotic administration guidelines

The following is based on current BNF guidelines:

### 1.Respiratory system

| Condition | Recommended treatment |
|---|---|
| Exacerbations of chronic bronchitis | **Amoxicillin or tetracycline or clarithromycin** |
| Uncomplicated community-acquired pneumonia | **Amoxicillin** (Doxycycline or clarithromycin in penicillin allergic, add flucloxacillin if staphylococci suspected e.g. In influenza) |
| Pneumonia possibly caused by atypical pathogens | **Clarithromycin** |
| Hospital-acquired pneumonia | Within 5 days of admission: co-amoxiclav or cefuroxime<br>More than 5 days after admission: piperacillin with tazobactam OR a broad-spectrum cephalosporin (e.g. ceftazidime) OR a quinolone (e.g. ciprofloxacin) |

### 2.Urinary tract

| Condition | Recommended treatment |
|---|---|
| Lower urinary tract infection | **Trimethoprim or nitrofurantoin.** Alternative: amoxicillin or cephalosporin |
| Acute pyelonephritis | **Broad-spectrum cephalosporin or quinolone** |
| Acute prostatitis | **Quinolone or trimethoprim** |

## 3.Skin

| Condition | Recommended treatment |
|---|---|
| Impetigo | **Topical hydrogen peroxide,** oral flucloxacillin or erythromycin if widespread |
| Cellulitis | **Flucloxacillin** (clarithromycin, erythromycin or doxycycline if penicillin-allergic) |
| Cellulitis (near the eyes or nose) | Co-amoxiclav (clarithromycin, + metronidazole if penicillin-allergic) |
| Erysipelas | Flucloxacillin* (clarithromycin, erythromycin or doxycycline if penicillin-allergic) |
| Animal or human bite | **Co-amoxiclav** (doxycycline + metronidazole if penicillin-allergic) |
| Mastitis during breast-feeding | Flucloxacillin |

## 4.Ear, nose & throat

| Condition | Recommended treatment |
|---|---|
| Throat infections | **Phenoxymethylpenicillin** (erythromycin alone if penicillin-allergic) |
| Sinusitis | **Phenoxymethylpenicillin** |
| Otitis media | **Amoxicillin** (erythromycin if penicillin-allergic) |
| Otitis externa** | **Flucloxacillin** (erythromycin if penicillin-allergic) |
| Periapical or periodontal abscess | **Amoxicillin** |
| Gingivitis: acute necrotising ulcerative | **Metronidazole** |

## 5.Genital system

| Condition | Recommended treatment |
|---|---|
| Gonorrhoea | **Intramuscular ceftriaxone** |
| Chlamydia | **Doxycycline or azithromycin** |
| Pelvic inflammatory disease | **Oral ofloxacin + oral metronidazole or intramuscular ceftriaxone + oral doxycycline + oral metronidazole** |
| Syphilis | **Benzathine benzylpenicillin or doxycycline or erythromycin** |
| Bacterial vaginosis | **Oral or topical metronidazole or topical clindamycin** |

## 6.Gastrointestinal

| Condition | Recommended treatment |
|---|---|
| Clostridium difficile | **First episode:** oral vancomycin<br>Second or subsequent episode of infection: oral fidaxomicin |
| Campylobacter enteritis | **Clarithromycin** |
| Salmonella (non-typhoid) | **Ciprofloxacin** |
| Shigellosis | **Ciprofloxacin** |

**a combined topical antibiotic and corticosteroid is generally used for mild/moderate cases of otitis externa**

# Antiviral agents

| Drug | Mechanism of action | Indications | Adverse effects/toxicity |
|---|---|---|---|
| **Aciclovir** | **Guanosine analog, phosphorylated by thymidine kinase which in turn inhibits the viral DNA polymerase** | HSV, VZV | **Crystalline nephropathy** |
| **Ganciclovir** | **Guanosine analog, phosphorylated by thymidine kinase which in turn inhibits the viral DNA polymerase** | CMV | **Myelosuppression / agranulocytosis** |
| **Ribavirin** | **Guanosine analog which inhibits inosine monophosphate (IMP) dehydrogenase, interferes with the capping of viral mRNA** | Chronic hepatitis C, RSV | **Haemolytic anaemia** |
| **Amantadine** | **Inhibits uncoating (M2 protein) of virus in cell. Also releases dopamine from nerve endings** | Influenza, Parkinson's disease | **Confusion, ataxia,** slurred speech |
| **Oseltamivir** | Inhibits neuraminidase | Influenza | |
| **Foscarnet** | Pyrophosphate analog which inhibits viiral DNA polymerase | CMV, HSV if not responding to aciclovir | **Nephrotoxicity,** hypocalcaemia, hypomagnasaemia, seizures |
| **Interferon-α** | Human glycoproteins which inhibit synthesis of mRNA | Chronic hepatitis B & C, hairy cell leukaemia | **Flu-like symptoms,** anorexia, myelosuppression |
| **Cidofovir** | Acyclic nucleoside phosphonate, and is therefore independent of phosphorylation by viral enzymes (compare and contrast with aciclovir/ganciclovir) | CMV retinitis in HIV | Nephrotoxicity |

## Anti-retroviral agent used in HIV

### Nucleoside analogue reverse transcriptase inhibitors (NRTI)

- examples: zidovudine (AZT), didanosine, lamivudine, stavudine, zalcitabine

### Protease inhibitors (PI)

- inhibits a protease needed to make the virus able to survive outside the cell
- examples: indinavir, nelfinavir, ritonavir, saquinavir

### Non-nucleoside reverse transcriptase inhibitors (NNRTI)

- examples: nevirapine, efavirenz

## Antifungal agents

| Drug | Mechanism of action | Adverse effects | Notes |
|---|---|---|---|
| Azoles | Inhibits 14α-demethylase which produces ergosterol | **P450 inhibition** Liver toxicity | |
| Amphotericin B | **Binds with ergosterol forming a transmembrane channel that leads to monovalent ion (K+, Na+, H+ and Cl) leakage** | **Nephrotoxicity,** flu-like symptoms, hypokalaemia, hypomagnaseamia | Used for systemic fungal infections |
| Terbinafine | **Inhibits squalene epoxidase** | | Commonly used in oral form to treat fungal nail infections |
| Griseofulvin | Interacts with microtubules to disrupt mitotic spindle | Induces P450 system, teratogenic | |
| Flucytosine | Converted by cytosine deaminase to 5-fluorouracil, which inhibits thymidylate synthase and disrupts fungal protein synthesis | Vomiting | |
| Caspofungin | Inhibits synthesis of beta-glucan, a major fungal cell wall component | Flushing | |
| Nystatin | Binds with ergosterol forming a transmembrane channel that leads to monovalent ion (K+, Na+, H+ and Cl) leakage | 1 | As very toxic can only be used topically (e.g. for oral thrush) |

## Incubation periods of different infectious agents

Questions may either ask directly about incubation periods or they may be used to provide a clue in a differential diagnosis.

| < 1 week | 1 - 2 weeks | 2 - 3 weeks | >3 weeks |
|---|---|---|---|
| • Influenza<br>• Diphtheria<br>• Scarlet fever<br>• Meningococcus | • Measles<br>• Malaria<br>• Typhoid fever<br>• Dengue fever | • Mumps<br>• Rubella<br>• Chickenpox | • Viral hepatitis<br>• HIV<br>• CMV<br>• IMN |

## Vaccinations

It is important to be aware of vaccines which are of the live-attenuated type as these may pose a risk to immunocompromised patients. The main types of vaccine are as follows:

### Live attenuated

- **BCG**
- measles, mumps, rubella **(MMR)**
- **influenza (intranasal)**
- **oral rotavirus**
- **oral polio**
- **yellow fever**
- **oral typhoid**

### Inactivated preparations

- **rabies**
- **hepatitis A**
- **influenza (intramuscular)**

### Toxoid (inactivated toxin)

- tetanus
- diphtheria
- pertussis

Subunit and conjugate vaccines are often grouped together.
Subunit means that only part of the pathogen is used to generate an immunogenic response.
A conjugate vaccine is a particular type that links the poorly immunogenic bacterial polysaccharide outer coats to proteins to make them more immunogenic

- **pneumococcus** (conjugate)
- **haemophilus** (conjugate)
- **meningococcus** (conjugate)
- **hepatitis B**
- **human papillomavirus**

## Notes

- influenza: different types are available, including whole inactivated virus, split virion (virus particles disrupted by detergent treatment) and sub-unit (mainly haemagglutinin and neuraminidase)
- cholera: contains inactivated Inaba and Ogawa strains of Vibrio cholerae together with recombinant B-subunit of the cholera toxin
- hepatitis B: contains HBsAg adsorbed onto aluminium hydroxide adjuvant and is prepared from yeast cells using recombinant DNA technology

## Splenectomised patients

- Splenectomised patients are at **increased risk of infection with**:
  - encapsulated bacteria
    - A popular mnemonic to remember most of the encapsulated bacteria is the **SHiNE SKiS** bacteria (**S**. pneumo, **Hib**, **N**. meningitidis, **E**. Coli, **S**almonella, **K**lebsiella, Group B **S**trep).
  - infections that are filtered by the spleen (for example, malaria).

## Prophylaxis in splenectomy

- Following a splenectomy patients are particularly at risk from pneumococcus, Haemophilus, meningococcus and Capnocytophaga canimorsus* infections
  - usually from dog bites

### Vaccination

- if elective, should be done 2 weeks prior to operation
- Hib, meningitis A & C
- annual influenza vaccination
- pneumococcal vaccine every 5 years
- Patients who have **emergency splenectomies** should be vaccinated post-operatively (most effective if performed **at least 14 days after surgery**)

### Antibiotic prophylaxis

- penicillin V: unfortunately clear guidelines do not exist of how long antibiotic prophylaxis should be continued. It is generally accepted though that penicillin should be continued for at least 2 years and at least until the patient is 16 years of age, although the majority of patients are usually put on antibiotic prophylaxis for life

**MRCPUK part 1 exam: H/O emergency splenectomy. Following this he takes penicillin V on a daily basis. He is unsure of his vaccination history. Which organism is he particularly suscepitble to?**
**>> *Haemophilus influenza*** *(Penicillin V would protect him against Streptococcus pneumoniae but notHaemophilus influenzae due to the production of beta-lactamases by the organism)*

**MRCPUK part 1 exam: A 12-year-old boy who had a splenectomy following RTA, he had his full immunisation course as a child and was given a repeat pneumococcal vaccination 5 days following surgery. What is the most appropriate ongoing management?**
**>> Booster dose of Hib and MenC vaccine + annual influenza vaccination + lifelong penicillin V**

## BCG vaccine

The Bacille Calmette-Guérin (BCG) vaccine offers limited protection against tuberculosis (TB). In the UK it is given to high-risk infants. Until 2005 it was also routinely given to children at the age of 13 years.

The Greenbook currently advises that the vaccine is administered to the following groups (below is summary, please see the link for more details):

- all infants (aged 0 to 12 months) living in areas of the UK where the annual incidence of TB is 40/100,000 or greater
- all infants (aged 0 to 12 months) with a parent or grandparent who was born in a country where the annual incidence of TB is 40/100,000 or greater. The same applies to older children but if they are 6 years old or older they require a tuberculin skin test first
- previously unvaccinated tuberculin-negative contacts of cases of respiratory TB
- previously unvaccinated, tuberculin-negative new entrants under 16 years of age who were born in or who have lived for a prolonged period (at least three months) in a country with an annual TB incidence of 40/100,000 or greater
- healthcare workers
- prison staff
- staff of care home for the elderly
- those who work with homeless people

The vaccine contains live attenuated Mycobacterium bovis. It also offers limited protection against leprosy.

### Administration

- any person being considered for the BCG vaccine must first be given a tuberculin skin test. The only exceptions are children < 6 years old who have had no contact with tuberculosis
- given intradermally, normally to the lateral aspect of the left upper arm
- BCG can be given at the same time as other live vaccines, but if not administered simultaneously there should be a 4 week interval

### Contraindications

- previous BCG vaccination
- a past history of tuberculosis
- HIV
- pregnancy
- positive tuberculin test (Heaf or Mantoux)

The BCG vaccine is not given to anyone over the age of 35, as there is no evidence that it works for people of this age group.

## Tetanus: vaccination

The tetanus vaccine is a cell-free purified toxin that is normally given as part of a combined vaccine.

Tetanus vaccine is currently given in the UK as part of the routine immunization schedule at:

- 2 months
- 3 months
- 4 months
- 3-5 years
- 13-18 years

This, therefore, provides 5 doses of tetanus-containing vaccine. Five doses is now considered to provide adequate long-term protection against tetanus.

### Management of wounds

The Greenbook contains the full criteria. The information below is only an abbreviated summary:

The first step is to classify the wound:

| Clean wound | Tetanus prone wound | High-risk tetanus prone wound |
|---|---|---|
| Wounds less than 6 hours old, non-penetrating with negligible tissue damage | • puncture-type injuries acquired in a contaminated environment e.g. gardening injuries<br>• wounds containing foreign bodies<br>• compound fractures<br>• wounds or burns with systemic sepsis<br>• certain animal bites and scratches | • heavy contamination with material likely to contain tetanus spores e.g. soil, manure<br>• wounds or burns that show extensive devitalised tissue<br>• wounds or burns that require surgical intervention |

**Patient has had a full course of tetanus vaccines, with the last dose < 10 years ago**

- **no vaccine nor tetanus immunoglobulin is required, regardless of the wound severity**

**Patient has had a full course of tetanus vaccines, with the last dose > 10 years ago**

- if tetanus prone wound: reinforcing dose of vaccine
- high-risk wounds (e.g. compound fractures, delayed surgical intervention, significant degree of devitalised tissue): reinforcing dose of vaccine + tetanus immunoglobulin

**If vaccination history is incomplete or unknown**

- reinforcing dose of vaccine, regardless of the wound severity
- for tetanus prone and high-risk wounds: reinforcing dose of vaccine + tetanus immunoglobulin

**Treatment**: to prevent the development of tetanus:
Clean wound + **I.M human tetanus immunoglobulin ± Tetanus vaccine ± Antibiotic (Metronidazole IV).**

**exam: H/O 4 cm laceration to the dorsum of left hand after cutting using a Stanley knife. no sign of a foreign body. He has 'no idea' about his tetanus vaccination. What is the most appropriate action with respect to tetanus?**

**>> Requires tetanus vaccine + complete vaccine course at a later date**

- **(This wound is not high risk for tetanus)**

# Bacteriology

## Staphylococci

Staphylococci are a common type of bacteria that are often found normal commensal organisms but may also cause invasive disease.

### Some basic facts include:

- Gram-positive cocci
- facultative anaerobes
- produce catalase
- **Staphylococci are skin organisms most commonly introduced during pacemaker insertion and such a discitis would present with back pain.**

### Coagulase test:

- used to differentiate between different Staphylococcus species
  - Coagulase-Positive Staph species:
    - **Staph aureus** is the most important of the coagulase positive Staphylococcus species and is highly pathogenic.
  - Coagulase-negative Staph species:
    - most likely to be skin commensal organisms of relatively low pathogenicity, such as Staph epidermidis or Staph saprophyticus, although some may still cause deeper infection or sepsis.

The two main types of Staphylococci you need to know about are Staphylococcus aureus and Staphylococcus epidermidis.

| Staphylococcus aureus | Staphylococcus epidermidis |
|---|---|
| • Coagulase-positive<br>• Causes skin infections (e.g. cellulitis), abscesses, osteomyelitis, toxic shock syndrome | • Coagulase-negative<br>• Cause of central line infections and infective endocarditis |

- **Nasal swabs should be routinely checked in patients with recurrent staphylococcal abscesses**
- **Recurrent skin infections** caused by **staphylococcus** often reflect **colonisation** that will require use of clearance procedures (body wash and topical nasal treatment) in order to prevent ongoing recurrences. This is particularly important in younger athletes in whom colonisation with resistant staphylococcal strains can occur.

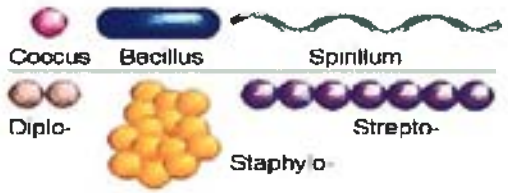
## Staphylococcus aureus

- catalase and coagulase positive, beta hemolytic organism.
- produces a yellow pigment ('Aureus' is Latin for 'gold'.)
- stained purple by gram staining.
- *Staphylococcus aureus* produce exotoxins that lead to three syndromes:
  1. food poisoning, caused by ingestion of *S. aureus* enterotoxin;
     - ***S. aureus*** is the most common cause of food poisoning.
     - The enterotoxin produced by *Staphylococcus aureus (heat stable toxin)* causes rapid-onset food poisoning.
       - Staph bacteria are killed by cooking, but the toxins are not destroyed
  2. scalded skin syndrome, caused by exfoliative toxin; (Exfoliatin A and B)
  3. toxic shock syndrome (TSS), caused by toxic shock syndrome toxin-1 (TSST-1)
- What is the mechanism by which methicillin-resistant *Staphylococcus aureus* gains resistance to penicillins?
  - Alterations in penicillin-binding proteins

## Effective antibiotics:

- Staphylococcal and streptococcal organisms are effectively treated by **semisynthetic penicillins**, including oxacillin, nafcillin, dicloxacillin, and **cloxacillin**. Also, first- and second-generation cephalosporin
- Penicillin G, **ampicillin**, and **amoxicillin**: These agents are effective against streptococci, such as S. pyogenes, viridans group streptococci, and S. pneumonia, **but not against staphylococci**
- Ampicillin and amoxicillin are only effective against staph when ampicillin is combined with the **beta-lactamase inhibitor sulbactam** or when amoxicillin is combined with **clavulanate**.

- The Gram stain shows Gram positive cocci **growing in clusters, typical of *Staphylococcus aureus*.**
- This is the most likely organism to cause post-operative infection of prosthetic joints within the first one to four weeks following surgery.



# MRSA

Methicillin-resistant Staphylococcus aureus (MRSA) was one of the first organisms which highlighted the dangers of hospital-acquired infections.

## Who should be screened for MRSA?

- All patients awaiting elective admissions (exceptions include day patients having terminations of pregnancy and ophthalmic surgery. Patients admitted to mental health trusts are also excluded).
- all emergency admissions will be screened.

## How should a patient be screened for MRSA?

- Nasal swab and skin lesions or wounds.
- The swab should be wiped around the inside rim of a patient's nose for 5 seconds.
- The microbiology form must be labelled 'MRSA screen'.

## Suppression of MRSA from a carrier once identified:

- **Nose**: mupirocin 2% in white soft paraffin, TID for 5 days.
- **Skin:** chlorhexidine gluconate, OD for 5 days. Apply all over but particularly to the axilla, groin and perineum.

## Treatment of MRSA infections:

- vancomycin
- teicoplanin
- linezolid

Some strains may be sensitive to the antibiotics listed below but **they should not generally be used alone** because resistance may develop:

**(i.e. to be used with vancomycin or Teicoplanin):**

- **Rifampicin**
- Macrolides
- Tetracyclines
- Aminoglycosides
- Clindamycin

Relatively new antibiotics such as linezolid, quinupristin/dalfopristin combinations and tigecycline have activity against MRSA but should be reserved for resistant cases.

**N.B:** Whilst tackling MRSA requires a multi-pronged approach the evidence base demonstrates that **hand hygiene** is the single most important step.

**NB**: **Aminoglycosides** may **impair neuromuscular transmission** and should **not** be given to patients with **myasthenia gravis**; large doses given during surgery have been responsible for a transient myasthenic syndrome in patients with normal neuromuscular function (**Aminoglycoside-induced neuromuscular blockade).**
Non-depolarising muscle relaxants (also known as competitive muscle relaxants) compete with acetylcholine for receptor sites at the neuromuscular junction. Non-depolarising muscle relaxants may be divided into the

- Aminosteroid group (ex; pancuronium, vecuronium), and the
- Benzylisoquinolinium group (ex: atracurium).

**EX**: A 23-year-old IV drug user presents with bilateral groin abscesses. After drainage of the abscesses he is started on **IV flucloxacillin and gentamicin**. **Twelve hours later** he complained of diplopia which deteriorated, and also developed dysphagia and muscle weakness and needed ventilatory support.
The diagnosis is >>> **Aminoglycoside-induced neuromuscular blockade.**

**MRCP UK part 1 exam**: **What is the most effective single step to reduce the incidence of MRSA?**
**>> Hand hygiene**

**MRCP UK part 1 exam: What is the most appropriate antibiotic regimen for possible line sepsis from an indwelling permacath?**
**>> Vancomycin + Gentamicin**
The antibiotic chosen should have both gram-positive and gram-negative cover, including MRSA.
vancomycin and doxycycline are able to treat MRSA, but doxycycline has limited gram-negative cover, unlike gentamicin.

## Streptococci

- Streptococci are gram-positive cocci.
- divided into alpha and beta haemolytic types

### α-Alpha haemolytic streptococci (Partial haemolysis):

- The most important alpha haemolytic *Streptococcus* is ***Streptococcus pneumoniae*** **(pneumococcus).**
- Pneumococcus is a common cause of pneumonia, meningitis and otitis media.
- Another clinical example is *Streptococcus viridans*

## β-Beta haemolytic streptococci (Complete haemolysis):

These can be subdivided into groups A-H. Only groups A, B & D are important in humans.

### Group A:

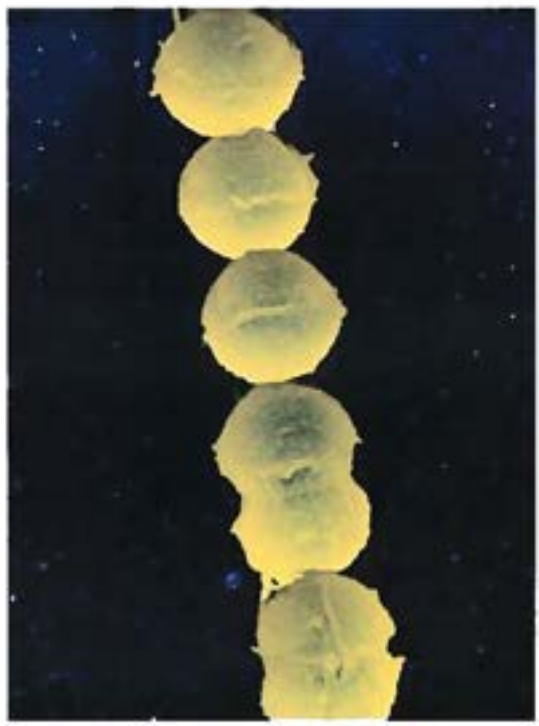
- Most important organism is ***Streptococcus pyogenes*:**
- Responsible for **erysipelas**, impetigo, **cellulitis, type 2 necrotizing fasciitis** and pharyngitis/tonsillitis.
- **Immunological** reactions can cause **rheumatic fever** or **post-streptococcal glomerulonephritis.**
- Erythrogenic toxins cause **scarlet fever.**
- **Penicillin is the antibiotic of choice for group A streptococcal infection.**

### Group B:

- Streptococcus agalactiae may lead to neonatal meningitis and septicaemia.
  - **Lipoteichoic acid is the primary virulence factor of this organism**

### Group D:

- *Enterococcus.*



Group B streptococcus bacteria. Credit: NIAID

# Enterococcus

## Classification

- Previously classified as group D streptococci
- In the 1980s, based on genetic differences, enterococci were removed from the genus Streptococcus and placed in their own genus, Enterococcus

## Enterococcus species

- E. faecalis: the predominant enterococcal species, 80 to 90% of all clinical isolates,
- E. faecium: 5 to 15%
- Others: (E. gallinarum, E. casseliflavus, E. durans, E. avium, and E raffinosis) less than 5%

## Importance.

- Enterococci are currently ascendant nosocomial pathogens, due to their intrinsic resistance to several commonly used antibiotics
  - the second most common organisms recovered from nosocomial urinary tract and wound infections
  - the third most common cause of nosocomial bacteremia in the United States

## Treatment

- Until recently, vancomycin was virtually the only drug that could be consistently relied on for the treatment of infections caused by multidrug-resistant enterococci.
  - Oral vancomycin, which is poorly absorbed, has been used extensively for the treatment of Clostridium difficile enterocolitis.

# Vancomycin-resistant enterococci

## Risk Factors

- patients in ICUs
- prolonged hospitalization
- patients with chronic renal failure, cancer, or organ transplant recipients,
- Vancomycin use has been reported consistently as a risk facior for colonization and infection with VRE and may increase the possibility of the emergence of vancomycin-resistant S. aureus or S. epidermidis.

### Modes of Transmission

- Transmission of VRE by health care workers whose hands become transiently contaminated with the organism while caring for affected patients is probably the most common mode of nosocomial transmission.

### Clinical problems

- When they cause clinical problems, they are usually urinary tract infections (UTI), bacteraemia, wound infections, neonatal infections, endocarditis, etc.

### Sources

- **May be found in healthy community volunteers not recently hospitalised**
- Community reservoir in meat, poultry and perhaps cheese.

### Mechanism of resistance

- Vancomycin-resistant enterococci alter peptidoglycan preCursors used to build cell walls. Vancomycin binds to D-ala-D-ala but the resistant enterocoCci havve D-ala-D-lac or D-ala terminating precursors.
- They acquire genes that produce enzymes to change the precursors.

### Treatment

- Teicoplanin is another glycopeptide antibiotic: Because of their activity against methicillin- resistant staphylococci and other gram-positive bacteria, these drugs have been widely used for therapy and prophylaxis against infections due to these organisms

## Clostridia

Clostridia are gram-positive, obligate anaerobic bacilli.

### C. perfringens

- produces α-toxin, a lecithinase, which causes gas gangrene (myonecrosis) and haemolysis
- features include tender, oedematous skin with haemorrhagic blebs and bullae. Crepitus may present on palpation

### C. botulinum

- typically seen in canned foods and honey
- prevents acetylcholine (ACh) release leading to **flaccid paralysis**

### C. difficile

- causes pseudomembranous colitis, typically seen after the use of broad-spectrum antibiotics
- produces both an exotoxin and a cytotoxin

### C. tetani

- produces an exotoxin (tetanospasmin) that prevents the release of glycine from Renshaw cells in the spinal cord causing a **spastic paralysis**

## Escherichia coli

Escherichia coli is a facultative anaerobic, lactose-fermenting, Gram negative rod which is a normal gut commensal.

### E. coli infections lead to a variety of diseases in humans including:

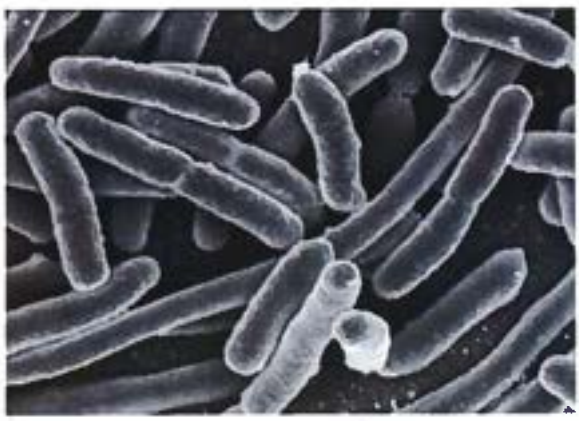
- diarrhoeal illnesses
- UTIs
- neonatal meningitis

### Serotypes

**E.** coli may be classified according to the antigens which may trigger an immune response:

| Antigen | Origin | Notes |
|---|---|---|
| **O** | Lipopolysaccharide layer | |
| **K** | Capsule | Neonatal meningitis secondary to E. coli is usually caused by a serotype that contains the capsular antigen K-1 |
| **H** | Flagellin | |

**E.** coli O157:H7 is a particular strain associated with severe, haemorrhagic, watery diarrhoea. It has a high mortality rate and can be complicated by haemolytic uraemic syndrome. It is often spread by contaminated ground beef.



Scanning electron micrograph of *Escherichia coli*, grown in culture and adhered to a cover slip. Credit: NIAID

# Listeria monocytogenes

## Tips:

**Listeria meningitis should always be considered in patients with meningitis associated with brain stem involvement, in elderly and in immunosuppressed patients.**

## Criteria:

- Listeria is a motile non-spore forming **Gram positive bacillus.**
- It has the unusual ability to multiply at **low** temperatures.
- It is typically spread via **contaminated food**, typically **unpasteurised dairy** products (**French soft cheese**).
- Infection is particularly dangerous to the unborn child where it can lead to miscarriage.

Listeria meningitis should always be considered in patients with **meningitis associated with brain stem involvement**, and in **immunosuppressed** patients.

**Features** - can present in a variety of ways:

- Diarrhoea, flu-like illness
- Pneumonia
- CNS infection as **meningoencephalitis** and even **hemiparesis mimicking a stroke.**
- **Ataxia** and seizures

Suspected Listeria infection should be investigated by taking **blood cultures. CSF** may reveal a pleocytosis, with 'tumbling motility' on wet mounts.

## Management:

- Listeria is **sensitive to amoxicillin/ampicillin** (cephalosporins usually inadequate).
- Listeria meningitis should be treated with **IV amoxicillin/ampicillin and gentamicin.**

### In pregnant women

- **pregnant women are almost 20 times more likely to develop listeriosis** compared with the rest of the population due to changes in the immune system
- fetal/neonatal infection can occur both transplacentally and vertically during child birth

- complications include miscarriage, premature labour, stillbirth and chorioamnionitis
- diagnosis can only be made from blood cultures
- treatment is with amoxicillin

## Pyogenic liver abscess

The most common organisms found in pyogenic liver abscesses are Staphylococcus aureus in children and **Escherichia coli in adults.**

### Management:

- **Drainage** (needle aspiration or catheter) should always be performed.
- **Amoxicillin + ciprofloxacin + metronidazole.**
- If penicillin allergic: ciprofloxacin + clindamycin.

**MRCP UK exam: What is the most appropriate antibiotic therapy to accompany drainage of liver abscess?**
**>>> Amoxicillin + ciprofloxacin + metronidazole**

## Tetanus

- Tetanus is caused by the tetanospasmin exotoxin released from Clostridium tetani.
- Tetanus spores are present in soil and may be introduced into the body from a wound, which is often unnoticed.
- Tetanospasmin prevents release of GABA.

**Incubation period: 3 - 21 days.**

### Pathophysiology

- C. tetani spores contaminate a wound (especially with animal feces and soil)production of the neurotoxins tetanospasmin and tetanolysin
- Tetanospasmin: reaches the CNS **through retrograde axonal transport >> cleaves a synaptobrevin protein** >> prevention of inhibitory neurotransmitters (i.e., GABA and glycine) >> tetanic spasms.
- Tetanolysin: causes hemolysis and has cardiotoxic effects
- The wound is often unnoticed (the absence of a wound does not exclude tetanus).

## Features:

- Prodrome fever, lethargy, headache
- **Trismus** (**lockjaw** or **jaw spasm**)
- **Risus sardonicus**
- **Opisthotonus** (arched back, hyperextended neck)
- Spasms (e.g. **dysphagia**)
- **Cephalic tetanus** means involving the cranial nerves usually from a wound on the head and neck. It causes severe dysphagia. It may be confused with rabies but hydrophobia never occurs.

## Diagnosis

- clinical diagnosis based on muscle spasms and rigidity associated with an entry point for bacteria and an inadequate vaccination history.

## Management

- **Supportive** ttt: including **ventilatory** support and **muscle relaxants.**
- **I.M human tetanus immunoglobulin** for high-risk wounds (e.g. compound fractures, delayed surgical intervention, significant degree of devitalised tissue).
- **I.V Metronidazole** is now preferred to **benzylpenicillin** as the antibiotic of choice.

**NB**: While Clostridium-specific intravenous immunoglobulin **IVIG** is **ineffective** once the toxin is attached to **nervous** tissue **it may prevent progression.**
**NB**: Absence of a wound does not exclude tetanus.

# Gas gangrene

It is caused by **Clostridium perfringens** (or other Clostridium spp).

Infection often follows trauma and contamination of the wound by soil containing clostridial spores.

Patients with gas gangrene tend to be more systemically unwell than the degree of cellulitis would suggest and urgent surgical attention may prevent death.

**Treatment**: **Urgent surgical debridement**, high dose **benzyl-penicillin** and **clindamycin**, and **hyperbaric oxygen** if available.

# Salmonella (Typhoid fever) (Enteric fever)

- The Salmonella group contains many members, most of which cause diarrhoeal diseases.
- They are **aerobic, Gram negative rods** which are **not normally** present as commensals in the gut.
- Typhoid and paratyphoid are caused by Salmonella typhi and Salmonella paratyphi (types A, B & C) respectively.
- They are often termed enteric fevers, producing systemic symptoms such as headache, fever, myalgia and arthralgia.
- Typhoid fever is seen in travellers returning from countries in the developing world e.g. India.
- Salmonella typhi has an **incubation period 1-3 weeks** followed by a prodrome of flu-like symptoms.
- It is often difficult to differentiate typhoid from malaria clinically.
- **Blood culture** is the **diagnostic** method of choice: **Gm –ve bacilli** of S. typhi.
- **Faecal culture** is positive in **only 50%** of cases during the **first week** of illness.
- **Serology by Widal test is not performed routinely in UK.**
- Vaccinated individuals who develop the disease will have a **higher** threshold but the same disease.

## Features:

- Initially systemic upset as above.
- **Fever with Relative bradycardia.**
- Abdominal pain, distension and possible hepatosplenomegaly.
- **Constipation**: **although Salmonella is a recognised cause of diarrhoea, constipation is more common in typhoid.**
- **Salmon-coloured rose spots**: present on the **trunk** in **40%** of patients, they are faint, maculopapular blanching lesions and are more common in paratyphoid.

### Possible complications include:

- Osteomyelitis (especially in sickle cell disease where Salmonella is one of the most common pathogens).
- GI bleed/perforation.
- Meningitis
- **Cholecystitis**: The gallbladder may act as a **reservoir** of infection and cause relapse in individuals treated with antibiotics. Cholecystectomy may be indicated.

- **Chronic carriage** (1%, **more likely if adult females**): Children are rarely chronic carriers of the organism although for some unknown reason females are more commonly long term carriers than males (remember: Typhoid Mary).

**The disease has stages as follow:**

| | |
|---|---|
| **Week 1** | Pyrexia and relative bradycardia |
| **Week 2** | • Maculopapular salmon-coloured rash that blanches on pressure.<br>• Hepatosplenomegaly.<br>• Lymphadenopathy. |
| **Week 3** | **Complications:**<br>• Lobar pneumonia<br>• Endocarditis<br>• Haemolytic anaemia<br>• GIT bleeding/perforation<br>• Meningitis<br>• Acute cholecystitis<br>• Osteomyelitis |

## Treatment:

- **Azithromycin** is usually preferred as the **oral** option for stable patient.
- **Ceftriaxone IV** for more **severe** disease.
- There is **extensive quinolones resistance** (reach to 80% in some areas).
- If the patient works in hospitality industry he should provide a negative specimen prior to returning to work.
- **In pregnancy or children, the drug of choice is parenteral ceftriaxone.**
- The gallbladder may act as a reservoir of infection and cause relapse in individuals treated with antibiotics. Cholecystectomy may be indicated.

# Shigella

## Overview:

- Shigella dysenteriae is a gram negative bacillus.
- Causes **bloody diarrhoea, abdominal pain.**
- Severity depends on type: S sonnei (e.g. from UK) may be mild, S flexneri or S dysenteriae from abroad may cause severe disease. Shigella infection is usually self-limiting and does not require antibiotic treatment
- antibiotics (e.g. **ciprofloxacin**) are indicated for people with severe disease, who are immunocompromised or with bloody diarrhoea

# Escherichia coli

Escherichia coli is a **facultative anaerobic**, lactose-fermenting, Gram negative rod which is a normal gut commensal.

**E. coli infections lead to a variety of diseases in humans including:**

- Diarrhoeal illnesses.
- UTIs.
- Neonatal meningitis.

**Serotypes:**

It is classified according to the antigens which may trigger an immune response:

| Antigen | Origin | Notes |
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| **O** | Lipopolysaccharide layer | |
| **K** | Capsule | Neonatal meningitis secondary to E. coli is usually caused by a serotype that contains the capsular antigen K-1 |
| **H** | Flagellin | |

**E. coli O157:H7** is a particular strain associated with severe, haemorrhagic, watery diarrhoea. It has a high mortality rate and can be complicated by **haemolytic uraemic syndrome (HUS)**. It is often spread by **contaminated ground beef**. The presentation is usually: **Diarrhea+ Renal imp+ ↓Hb+ ↓PLT**.

**multiple drug resistant Escherichia coli: mechanism of resistance**

**>> Extended spectrum beta-lactamase (ESBL) production**

- Some *E. coli* isolates produce an Extended spectrum beta-lactamase (ESBL) that inactivates second and third generation cephalosporins.

- The class of drugs that will most reliably treat these infections are the carbapenems.
- Extended spectrum B-lactamase (ESBL) producing organisms are typically resistant to penicillins and cephalosporins and as such the **carbapenem class of antibiotics are typically first line** although nitrofurantoin or fosfomycin are also frequently effective.
- ESBL producers are most commonly *Escherichia coli* (E. coli) and *Klebsiella* species.

**Which virulence factor contributes to the pathophysiology of the (E. coli) causing UTI?**

**>> P pilus**

- Uropathogenic E. coli utilize a **P pilus** to bind to uroepithelial cells and colonize the urethra.

## Campylobacter

- Campylobacter is the commonest bacterial cause of infectious intestinal disease in the UK.
- The majority of cases are caused by the Gram-negative bacillus Campylobacter jejuni.
- It is spread by the faecal-oral route
- has an incubation period of 1-6 days.

### Features

- prodrome: headache malaise
- diarrhoea: often bloody
- abdominal pain: may mimic appendicitis

### Management

- usually self-limiting
- **the most appropriate therapy is IV fluids.** appropriate fluid replacement and anti-emetics are initially indicated
- the BNF advises treatment if severe or the patient is immunocompromised. Clinical Knowledge summaries also recommend antibiotics if severe symptoms (high fever, bloody diarrhoea, or more than eight stools per day) or symptoms have last more than one week
- the first-line antibiotic is **clarithromycin**
- ciprofloxacin is an alternative although the BNF states that *'Strains with decreased sensitivity to ciprofloxacin isolated frequently'*

### Complications

- Guillain-Barre syndrome may follow *Campylobacter jejuni* infections
- reactive arthritis
- septicaemia, endocarditis, arthritis

# Mycobacteria

## Tuberculosis (TB)

- Tuberculosis (TB) is the ninth leading cause of death worldwide (WHO).
- Pulmonary tuberculosis is an infectious disease caused by *Mycobacterium tuberculosis*.
- Rarely, it may be due to *Mycobacterium bovis* or *Mycobacterium africanum*.
- In many cases, TB may remain dormant before it progresses to its active form.
- It most commonly involves the lungs and is communicable in this form, but may affect almost any organ system including the lymph nodes, CNS, liver, bones, genitourinary tract, and gastrointestinal tract.

### Epidemiology

- Tuberculosis mostly affects adults in their most productive years.
- Over 95% of cases and deaths are in developing countries
- In the US, an estimated 9.5 million people have latent TB infection

### Tuberculosis: types

- Tuberculosis (TB) is an infection caused by *Mycobacterium tuberculosis* that most commonly affects the lungs. Understanding the pathophysiology of TB can be difficult - the key is to differentiate between primary and secondary disease.

#### Primary tuberculosis

- A non-immune host who is exposed to *M. tuberculosis* may develop a primary infection of the lungs.
- A small lung lesion known as a Ghon focus develops.
- The Ghon focus is composed of tubercle-laden macrophages. The combination of a Ghon focus and hilar lymph nodes is known as a Ghon complex
- In immunocompetent people, the initial lesion usually heals by fibrosis.
- Those who are immunocompromised may develop disseminated disease (miliary tuberculosis).

#### Secondary (post-primary) tuberculosis

- If the host becomes immunocompromised the initial infection may become reactivated.
- Reactivation generally occurs in the apex of the lungs and may spread locally or to more distant sites.

**Possible causes of immunocompromise include:**

- immunosuppressive drugs including steroids
- HIV
- malnutrition

**The lungs remain the most common site for secondary tuberculosis.**

**Extra-pulmonary infection may occur in the following areas:**

- central nervous system (tuberculous meningitis - the most serious complication)
- vertebral bodies (Pott's disease)
- cervical lymph nodes (scrofuloderma)
- renal
- gastrointestinal tract

## Risk factors - Strong

- Having lived in Asia, Latin America, Eastern Europe, or Africa for years
- Exposure to an infectious TB case
- People who are infected with HIV are 20 to 30 times more likely to develop active TB
- Immunocompromised individuals (diabetics, patients on immunosuppressive therapy, malnourished, or those with haematological malignancies)
- Silicosis
- Apical fibrosis

## Risk factors - Weak

- Malignancy
- End-stage renal disease
- IV drug use
- Malnutrition
- Alcoholism
- Congested residence i.e. nursing homes, homeless shelters etc..
- Smoking

## Key diagnostic features:

### Common

- Presence of risk factors (see above)
- Cough: initially dry later productive (50% of patients had cough over 2 weeks - [1])
- Low-grade fever. ~20% may have no fever.
- Night sweats, if present usually drenching
- Anorexia
- Malaise ; may only be noticed in hindsight, after treatment

### Uncommon

- Pleuritic chest pain
- Haemoptysis ; present in <10% patients (typically with advanced disease) - may be as a result of complication such as bronchiectasis and not representative of active disease.
- Dyspnoea ; a late finding in the setting of extensive lung destruction or effusion
- Weight loss
- Psychological symptoms; depression or hypomania
- Patient may be asymptomatic and diagnosis made from coincidental findings or screening
- **hypoadrenalism**

## Signs:

- Chest examination may be normal in mild/moderate disease. Possible findings include crackles, bronchial breath sounds, or amphoric breath sounds (distant hollow breath sounds heard over cavities).
- Clubbing - if longstanding disease
- Erythema nodosum

## Transmission

- **Non-sputum producing patients are non-infectious** . Only untreated smear-positive pulmonary TB is likely to be infectious.

## Diagnosis of active tuberculosis

### Chest x-ray

- upper lobe cavitation is the classical finding of reactivated TB
- bilateral hilar lymphadenopathy

### Sputum smear

- 3 specimens are needed
- rapid and inexpensive test
- stained for the presence of acid-fast bacilli (Ziehl-Neelsen stain)
  - all mycobacteria will stain positive (i.e. nontuberculous mycobacteria)
- the sensitivity is between 50-80%
  - this is decreased in individuals with HIV to around 20-30%

### Sputum culture

- the gold standard investigation
  - more sensitive than a sputum smear and nucleic acid amplification tests
  - can assess drug sensitivities
- can take 1-3 weeks (if using liquid media, longer if solid media)

### Nucleic acid amplification tests (NAAT)

- allows rapid diagnosis (within 24-48 hours)
- more sensitive than smear but less sensitive than culture

## Investigations:

- If there is clinical suspicion of TB, the patient should be isolated
- Chest x-ray: Fibronodular opacities in upper lobes with or without cavitation
- Sputum acid-fast bacilli (AFB) smear (3 sputum samples): Positive for acid-fast bacilli
- Sputum culture: most sensitive and specific test. Should always be performed: positive in TB
- FBC: Raised WBC; low Hb
- Nucleic acid amplification tests (NAAT)(on at least one of the sputum samples): positive for Mycobacterium tuberculosis
- It is recommended that all patients with TB have an HIV test within 2 months of diagnosis of TB
- if the diagnosis is clinical then this should be stated

People who should be screened for TB include those born in high-incidence countries, HIV patients, intravenous drug users, health care workers who serve high-risk populations, and contacts of individuals with pulmonary TB. A tuberculin skin test or interferon gamma release assay are the standard methods for identifying persons infected with the mycobacterium. Screening persons other than high-risk population places a burden on resources and is therefore not recommended.

## Tuberculosis: screening

The two main tests used for screening in the UK are the **Mantoux (skin) test** and the **interferon-gamma (blood) test.**

Whilst the use of the interferon-gamma test is increasing it is still reserved for specific situations.

The **Mantoux test** is the **main** technique used **to screen for latent tuberculosis.**

One of its uses is for **patients who have had close contact with** a person known to have tuberculosis.

It is a **cell-mediated** immune response. It measures the **T cell**-mediated immune response to TB antigen. Immune complexes are not involved.

In recent years the **interferon-gamma** blood test has also been introduced. It is used in a number of specific situations such as:

- The Mantoux test is positive or equivocal
- People where a tuberculin test may be falsely negative (see below)

Tuberculin skin tests are an example of **type IV (delayed) hypersensitivity** reactions. These are largely mediated by **interferon-γ** secreted by **Th1 cells** which in turn stimulates macrophage activity.

The treatment for **latent tuberculosis** (i.e. Pt with +ve Tuberculin skin Mantoux test and had history of contact to a person proved to have TB) is **INH alone for 6 months** or **dual Rifampicin + INH for 3 months.**

### Mantoux test:

- 0.1 ml of 1:1,000 purified protein derivative (PPD) injected **intradermally** the **left forearm** is typically used.
- Result read **2-3 days later**: Only the **induration**, **not** surrounding erythema, is used in the measurement and the longest diameter is measured in millimetres:

| Diameter of induration | Positivity | Interpretation |
|---|---|---|
| **< 6mm** | **Negative** - no significant hypersensitivity to tuberculin protein | Previously **unvaccinated** individuals may be given the BCG (within 3 months) provided there are no contraindications. |
| **6 - 15mm** | **Positive** - hypersensitive to tuberculin protein | Should not be given BCG. May be due to **previous** TB infection or BCG or atypical mycobacteria. |
| **> 15mm** | **Strongly positive** - strongly hypersensitive to tuberculin protein | Suggests **tuberculosis** infection >> for further investigation (Sputum AFB) |

### False negative tests may be caused by:

- **Miliary TB**
- Sarcoidosis
- Immunosuppression
- **HIV**
- Viral infections
- Corticosteroids
- Lymphoma
- Very young age (e.g. < 6 months)

### Heaf test:

The Heaf test was previously used in the UK but has been since been discontinued. It is no longer used in the UK.

The Mantoux test replaced the Heaf test in 2005 in the UK

It involved injection of PPD equivalent to 100,000 units per ml to the skin over the flexor surface of the left forearm. It was then read 3-10 days later.

### Important notes for TB:

Sputum AFP stain +ve with negative culture >>> Atypical AFB such as M. avium

**Primary TB** is usually **asymptomatic.**

**Miliary TB** is the **most likely to occur** in **young children**.

**Primary pulmonary tuberculosis** is often **asymptomatic** consisting of primary complex.

**Cavitation and pleural effusions** are manifestations of **post primary TB.**

The **Ghon focus** is the area of consolidation from cellular infiltration and response to uptake of organisms by macrophages which transform into epithelioid cells and group into granulomata.

Bacilli are transported via **lymphatics early** in the disease process to regional lymph nodes to cause **marked lymphadenopathy**.

Pleural and pericardial infections (which can result in **effusions**) occur **at or shortly after primary infection.**

**Positive tuberculin test** occurs between **3 weeks** and **3 months** after primary infection.

So, **Pleural effusion may occurs before tuberculin skin testing is positive**.

**Non-sputum** producing patients are **non-infectious**.

All forms of pulmonary TB may be treated equally except tuberculous **pleural effusion** which may require **drainage** (with large effusions causing breathlessness) and adjunct corticosteroids to delay reaccumulation.

So lymph node positive disease **does** not requires longer treatment than pulmonary disease.

TB pleural effusion is **small to moderate effusion** rich in **lymphocytes.**

**Pleural effusion AAFB** (Acid Alkali Fast Bacilli) ZN stain are positive in **only 5-10%** (i.e. **it may be TB effusion with negative AFB**) and pleural effusion cultures are positive in **25-50%** of cases over 2-6 weeks and **pleural biopsy culture** is positive in **75%.**

Pleural biopsy histology may demonstrates granulomas, but has a lower sensitivity than culture cannot give bacterial sensitivities.

So the most useful test for the highest pick-up rate for pleural TB diagnosis is >>> **Pleural biopsy culture** (NOT histology or effusion culture of effusion AFB).

**Pleural biopsy culture and histology** give a total diagnostic rate of **90%.**

Pleural effusion **ADA** (Adenosine deaminase) is often raised in TB, but **not specific** as it can be raised in empyema, rheumatoid pleurisy and malignancy.

**EX:** Pt with HIV and pleural effusion with suspected TB >>> **Pleural biopsy culture and histology.**

Pleural fluid volume may increase during anti-TB therapy, **Corticosteroids** are associated with **reduced fluid volume** but have no effect on outcome, and pleural thickening and calcification unfortunately occurs commonly.

The treatment of **TB mediastinal lymphadenitis** is the **same** as **pulmonary** TB.

Length of treatment for other forms are:
- **Bone** TB - **9 months**
- **Meningitis - 1 year**
- Drug resistance - minimum of **9 months after** –ve sputum **up to 2 years**.

**Pyrazinamide** have high activity against **intracellular** organisms.
**Streptomycin** has high activity against **extracellular** organisms.

The phenomenon of a **'paradoxical reaction' during treatment for TB** has been recognised for many years. This can result in new lesions, or worsening of existing lesions. It is unpredictable in its timing, and can occur anything from a few days to many months after the start of treatment. Duration and severity is highly variable, and it can be **difficult to differentiate from** treatment failure, drug resistance or a superadded infection. Most cases are recognised in the setting of **lymph node** or **cerebral** disease. LN enlargement is seen in **30%** of cases. Occurrences are usually self-limiting.

**Corticosteroids** are effective in **reducing lymph node enlargement** and inflammation, and hence will help the stridor and breathlessness.

The diagnosis is already known, therefore mediastinoscopy and biopsy will not give any extra information.

**EX:** Pt with TB of the mediastinal lymph nodes and started anti-TB chemotherapy then developed increasing dyspnoea and stridor dt more LN enlargement at carina >>> TTT: **Corticosteroid**.

**Miliary TB:**

- **15 to 20%** of patients who have **military TB also have TB meningitis** at the **time** of presentation. Conversely 33% of patient with TB meningitis have concomitant miliary TB.

- The **tuberculin test** is often **negative**, so **a negative tuberculin test does not exclude diagnosis of miliary TB.**

- A **chest x ray may** be **normal** in up to **one third** of patients, so **normal CXR does not exclude diagnosis of miliary TB.**

- The classic **millet seed nodules** are **small** measuring about **1-2 mm**.

Mycobacterium **tuberculosis** and Mycobacterium **bovis** are classified as **'typical'** mycobacteria that cause a similar spectrum of disease.

As its name suggests, M. **bovis** also causes disease in **cattle** and the usual source of human infection was from **drinking contaminated milk**; this is now **rare**.

**BCG** (Bacillus Calmette-Guérin) is a **live attenuated** vaccine derived from a **strain of M. bovis**.

**BCG** is currently used as a form of immunotherapy for treating **bladder cancer**; several cases of disseminated M. bovis infection (systemic 'BCG-it is') have been described as a result of systemic infection following this treatment.

The **non-tuberculous mycobacteria (NTM)**; sometimes referred to as **'atypical'** mycobacteria. They differ from M. tuberculosis in that they are ubiquitous organisms and **have no person-to-person spread.**

Mycobacterium **avium** (also known as Mycobacterium **avium complex** [**MAC**], or Mycobacterium avium intracellulare [**MAI**]) causes

disseminated infection in patients with advanced **HIV**, typically when the **CD4** count is **less than 50** cells/mm$^3$.

This is a disseminated infection that usually causes symptoms of fatigue, weight loss and fevers. **Bone marrow infiltration** is typical and patients are often anaemic and/or **pancytopaenic**. The diagnosis is best made from bone marrow **aspiration and culture**. It may also be detected in blood cultures.

**EX**: Pt with **HIV**, fever, loss of weight, **CD 20 cells/mm$^3$**. **Pancytopenia**, bone marrow **aspirate** showed acid/alcohol fast bacilli (**AFB**) on light microscopy >>> so Mycobacterium **avium**

M. **fortuitum**, and M. **chelonae** typically present as **painful papular, nodular** or ulcerating **skin** lesions. Both are classified as a rapidly growing mycobacteria and infect immunocompetent individuals. It is a natural environmental organism that has been found in water sources, sewage and dirt.

Other manifestations include osteomyelitis, lymphadenitis, and ocular disease (keratitis and corneal ulceration), usually a result of wound contamination after trauma.

Disseminated disease may be seen in immunosuppressed patients.

**Mycobacterium marinum** infection occurs when contaminated water is exposed to skin that has experienced open trauma. It is an uncommon infection that is usually seen in patients who handle fish or swim in freshwater or saltwater. The skin is the most common site of infection, where it usually produces a solitary indolent granulomatous lesion - the **'fish tank granuloma'**. **Treatment**: **tetracyclines, fluoroquinolones, sulfonamides and macrolides.**

## Tuberculosis: drug therapy

- The standard therapy for treating **active tuberculosis** is:

  **Initial phase - first 2 months (RIPE):**

  1) **R**ifampicin.
  2) **I**soniazid.
  3) **P**yrazinamide.
  4) **E**thambutol (the 2019 NICE guidelines now recommend giving a 'fourth drug' such as Ethambutol routinely - previously this was only added if drug-resistant tuberculosis was suspected).

  **Continuation phase - next 4 months:**

  1) Rifampicin
  2) Isoniazid

- Patients with **meningeal tuberculosis** are treated for a prolonged period (**at least 12 months**) with the addition of **steroids.**
- **Directly observed therapy (DOT)** with **a three times a week** dosing regimen may be indicated in certain groups, including:
  - **Homeless** people with **active** tuberculosis.
  - Patients who are likely to have **poor concordance.**
  - All **prisoners** with **active or latent** tuberculosis.

**N.B: Streptomycin is used in resistant TB.**

**Multi-drug-resistant TB (MDR-TB):**

- As the name suggests is Mycobacterium tuberculosis resistant to 2 or more first line agents, which most commonly are rifampicin and isoniazid.
- There can be mono-resistance to each of the first line agents, but this is not MDR-TB.
- Risk factors for acquiring MDR-TB include previous TB treatment, HIV infection, contact with drug resistant disease and treatment failure.
- Treatment of MDR-TB is complex and time consuming.
- Treatment must be continued for a **minimum of 18 months**, with **at least 9 months of ttt after the patient becomes culture-negative.**
- Initial treatment includes **the use of 5 agents until sputum is negative** and **then continuation of 3 to which the TB is sensitive to for a minimum of 9 months** but sometimes up to 24 months.
- The minimum overall duration of ttt for MDR-TB once the sputum is negative is **9 months.**

## Tuberculosis: drug side-effects and mechanism of action

**Rifampicin:**

- Mechanism of action: inhibits bacterial DNA dependent **R**NA polymerase **preventing transcription of DNA into mRNA.**
- Potent liver enzyme **inducer.**
- Hepatitis.
- Orange secretions.
- Flu-like symptoms.

**Isoniazid (INH):**

- Mechanism of action: inhibits mycolic acid synthesis
- Liver enzyme **inhibitor**
- Hepatitis, agranulocytosis
- **Peripheral neuropathy:** prevent with pyridoxine (Vitamin **B6**). PN is particularly used in patients with **HIV** or **alcoholics.**
- **Tonic clonic convulsions**: Treatment: Diazepam & Vit B6 IV.

Pyridoxine is required as a cofactor in the manufacture of porphyrins for the synthesis of Hb >>> non Fe deficiency microcytic anaemia.
Pyridoxine causes an increase in the peripheral metabolism of Levodopa.
So **patient has both TB and Parkinsonism** with **anaemia** (non Fe def. microcytic anaemia) **>>> so ttt of his anaemia with pyridoxine will worsen the Parkinsonism.**

**Isoniazid toxicity** should be suspected in any patient with **intractable seizures** and **profound metabolic acidosis** with an elevated anion gap.

Isoniazid monotherapy is used for prevention of active TB in individuals with proven exposure to M. tuberculosis.

**Pyrazinamide**

- Mechanism of action: converted by pyrazinamidase into pyrazinoic acid which in turn inhibits fatty acid synthase (FAS) I
- Hyperuricaemia causing gout (There are case reports of Ethambutol-induced gout but it is not listed as a side-effect in the BNF).
- **Hepatitis**.
- **It should not be used in patient with known chronic liver disease**

**Ethambutol**

- Mechanism of action: inhibits the enzyme arabinosyl transferase which polymerizes arabinose into arabinan.
- **Optic neuritis** and **red-green colour blindness** due to optic neuropathy (but not cortical blindness).
- During the early stages of optic neuritis, **fundoscopy may will be normal**, and patients complain of slowly deteriorating visual acuity and loss of colour differentiation.
- So check **visual acuity** before and during treatment.
- Recoverability of vision after discontinuation of ethambutol therapy is the subject of some debate.
- **Dose adjustment** in patients with **renal impairment.**

**Streptomycin:**

- Vestibular damage → Vertigo and Vomiting
- Cochlear damage → deafness
- Nephrotoxicity
- Angioneurotic oedema

All tuberculosis patients should have pre-treatment LFTs.

If there is no pre-existing liver disease, LFTs are only repeated (and treatment stopped) if fever, malaise, vomiting, jaundice or unexplained deterioration occurs during treatment.

Regular LFTs should be performed in patients with previously known chronic liver disease. If AST/ALT levels rise by **five** times normal/ bilirubin level rises, then **rifampicin/isoniazid/pyrazinamide should be stopped.**

- If the patient is not unwell and/or has non-infectious TB, **no** treatment until LFT returns to normal.
- If clinically unwell or sputum smear is positive within 2 weeks of starting treatment, **consider streptomycin and Ethambutol until LFT returns to normal**.

**Once** LFT is back to normal, **challenge** dosages can be reintroduced sequentially in order of isoniazid, rifampicin and pyrazinamide with **daily** monitoring of patient's condition and LFT.

If there is a further reaction the offending drug should be excluded and a suitable alternative regimen used.

The metabolism of corticosteroids is increased by rifampicin, so patients on long term steroids should have their **dose of steroids increased** when starting antituberculous therapy.

**EX**: Pt with Anti-TB ttt (Rifampicin + INH + Pyrazinamide) for 2 months with elevated AST, ALT, ALP and bilirubin >>> so >>> **STOP ALL treatments**.

### Immune reconstitution disease

- occurs typically 3-6 weeks after starting treatment
- often presents with enlarging lymph nodes

## Leprosy (Hansen's disease) (HD)

It is a chronic disease caused by Mycobacterium leprae and Mycobacterium lepromatosis.
Clinical leprosy lies between 2 extremes: **Tuberculoid (TT)** and between the 2 ends of the spectrum lies a broad group designated as borderline and sub-classified as borderline tuberculoid (BT), midborderline (BB) and borderline lepromatous (BL).
The disease does not remain static but evolves spontaneously or in response to therapy.

### Features:

- Nodular skin lesion.
- Erythematous raised plaque like lesions in **arms** and legs.
- If left untreated >> progressive leprosy >> permanent damage to the skin, nerves, limbs and eyes.

## TIPS

- **patches of hypopigmented skin** typically affecting the buttocks, face, and extensor surfaces of limbs
- sensory loss

The degree of cell mediated immunity determines the type of leprosy a patient will develop.

**Low degree of cell mediated immunity → lepromatous leprosy ('multibacillary')**

- extensive skin involvement
- symmetrical nerve involvement

**High degree of cell mediated immunity → tuberculoid leprosy ('paucibacillary')**

- limited skin disease
- asymmetric nerve involvement → hypesthesia
- hair loss

## Diagnosis:

- PCR.
- Nerve conduction study: segmental slowing at the site of nerve entrapment.
- Skin biopsy.

## Management:

- **Skin biopsy** and needle test in cold area (ear lobe and elbow).
- **Pauci**-bacillary leprosy (< 5 lesions) >> ttt: Rifampicin+Dapsone for 6 m.
- **Multi**- bacillary leprosy (>5lesions)>>ttt: Rifampicin+Dapsone+Clofazimine for 12 m.

**NB**: BCG vaccine also give an immunity against leprosy ☺

# Sepsis Syndrome

## Staphylococcal toxic shock syndrome (STSS)

Staphylococcal toxic shock syndrome describes a severe systemic reaction to **staphylococcal exotoxins** (TSS-1, TSS-2).

It came to prominence in the early 1980's following a series of cases related to infected **tampons.**

The toxin damages vascular endothelium and triggers release of vasoactive agents from leucocytes and platelets, this increases vascular permeability and contributes to tissue damage.

Staphylococci may be cultured from high vaginal swabs.

Mortality remains approximately 10%.

Although the earliest described cases involved mostly menstruating women using highly absorbent tampons, only 55% of current cases are associated with menstruation. The illness can also occur in children, postmenopausal women, and men.

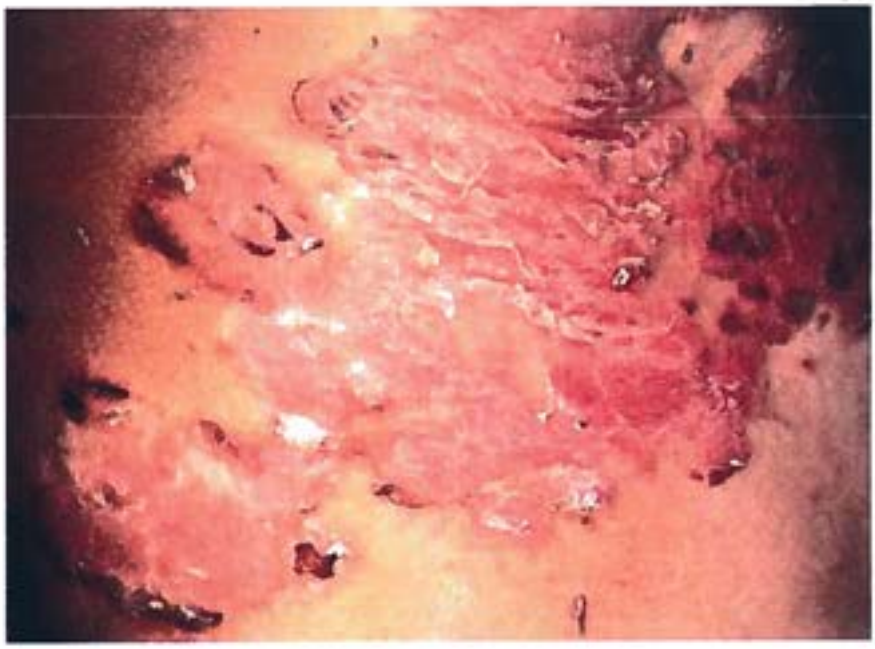
### Risk factors include:

- **Recent menstruation**
- Recent use of barrier contraceptives such as diaphragms and vaginal sponges
- **Vaginal tampon** use (especially prolonged)
- Recent childbirth
- **Recent surgery,** and
- Current S. aureus infection.

### Centres for Disease Control and Prevention diagnostic criteria:

- **Fever**: temperature > 38.9°C.
- **Hypotension**: systolic blood pressure < 90 mmHg.
- **Diffuse erythematous rash** (resembling sunburn) that peels after 1 to 2 weeks.
- **Desquamation** of rash, especially of the palms and soles.
- Involvement of **3 or more organ systems**: e.g. gastrointestinal (diarrhoea and vomiting), mucous membrane erythema, renal failure, hepatitis, thrombocytopenia, CNS involvement (e.g. confusion).

Blood cultures may be positive for S. aureus.



## Management

- Removal of the tampons if present.
- Anti-staphylococcal antibiotics e.g. vancomycin or flucloxacillin.
- IV fluids

**EX:** A 44-year-old farmer presents to the Emergency Department due to a **high temperature** and **confusion**. On examination his pulse is 124 bpm, BP **84/56** mmHg and **temperature 39.8°C**. He has a **generalised erythematous rash** which is starting to **desquamate on his palms** and is also noted to have a **paronychial infection of a fingernail** on the left hand. The most likely diagnosis **>> SSS**.

**EX:** A 16 years female with manifestations of acute gastroenteritis with high fever 40 C, hypotension BP 70/30 mmHg and rash **>>> TSS.**

# Sepsis

- Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to an infection.
- Sepsis is increasingly recognised as an important cause of mortality in the UK and there has been increasing efforts recently to improve the care of patients who present with sepsis.

**How sepsis is classified has changed in recent years - the Surviving Sepsis Guidelines were updated in 2017.**

**The new guidelines recognise the following terms:**

- **sepsis**: life-threatening organ dysfunction caused by a dysregulated host response to infection
- **septic shock**: a more severe form sepsis, technically defined as *'in which circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone'**

**The old category of severe sepsis is no longer used.**

- The term 'systemic inflammatory response syndrome (SIRS)' has also fallen out of favour.
- Adult patients outside of ICU with suspected infection are identified as being at heightened risk of mortality if they have quickSOFA (qSOFA) score meeting >= 2 of the following criteria:
  respiratory rate of 22/min or greater, altered mentation, or systolic blood pressure of 100mmHg or less

**qSOFA score**

- **Respiratory rate > 22/min**
- **Altered mentation**
- **Systolic blood pressure < 100 mm Hg**

Within an ICU setting a full SOFA** score is often used. Details can be found at the bottom of the notes.

## Management

NICE released their own guidelines in 2016. These focussed on the risk stratification and management of patients with suspected.

For risk stratification NICE recommend using the following criteria:

| Red flag criteria | Amber flag criteria |
|---|---|
| • Responds only to voice or pain/ unresponsive<br>• Acute confusional state<br>• Systolic B.P <= 90 mmHg (or drop >40 from normal)<br>• Heart rate > 130 per minute<br>• Respiratory rate >= 25 per minute<br>• Needs oxygen to keep SpO2 >=92%<br>• Non-blanching rash, mottled/ ashen/ cyanotic<br>• Not passed urine in last 18 h/ UO < 0.5 ml/kg/hr<br>• Lactate >=2 mmol/l<br>• Recent chemotherapy | • Relatives concerned about mental status<br>• Acute deterioration in functional ability<br>• Immunosuppressed<br>• Trauma/ surgery/ procedure in last 6 weeks<br>• Respiratory rate 21-24<br>• Systolic B.P 91-100 mmHg<br>• Heart rate 91-130 OR new dysrhythmia<br>• Not passed urine in last 12-18 hours<br>• Temperature < 36°C<br>• Clinical signs of wound, device or skin infection |

Clearly the underlying cause of the patients sepsis needs to be identified and treated and the patient supported regardless of the cause or severity. If however any of the red flags are present the 'sepsis six' should be started straight away:

1) Administer oxygen: Aim to keep saturations > 94% (88-92% if at risk of $CO_2$ retention e.g. COPD)
2) Take blood cultures
3) Give broad spectrum antibiotics
4) Give intravenous fluid challenges: NICE recommend a bolus of 500ml crystalloid over less than 15 minutes
5) Measure serum lactate
6) Measure accurate hourly urine output

**these patients can be clinically identified by a vasopressor requirement to maintain a MAP ≥ 65mmHg and serum lactate >2mmol/L in the absence of hypovolemia**

- To help identify and categorise patients the Sequential (Sepsis-Related) Organ Failure Assessment Score (SOFA) is increasingly used.

The score grades abnormality by organ system and accounts for clinical interventions. However, laboratory variables, namely, $PaO_2$, platelet count, creatinine level, and bilirubin level, are needed for full computation.

**SOFA Score**

| System | Score 0 | Score 1 | Score 2 | Score 3 | Score 4 |
|---|---|---|---|---|---|
| $PaO_2$ /Fl $O_2$ | >400 | <400 | <300 | <200 | <100 |
| Platelets x$10^3$ microlitres | >150 | <150 | <100 | <50 | <20 |
| Bilirubin µmol/L | 20 | 20-32 | 33-101 | 102-204 | >204 |
| Cardiovascular | MAP >70mmHg | MAP 70mmHg | Dopamine <5 or dobutamine (any dose) | Dopamine 5.1-15 or epinephrine 0.1 or norepinephrine 0.1 | Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1 |
| GCS | 15 | 13-14 | 10-12 | 6-9 | <6 |
| Creatinine µmol/L | <110 | 110-170 | 171-299 | 300-440 | >440 |
| Urine output ml/day | >500 | >500 | >500 | <500 | <200 |

A SOFA score of 2 or more reflects an overall mortality risk of approximately 10% in a general hospital population with suspected infection.
Even patients presenting with modest dysfunction can deteriorate further, emphasizing the seriousness of this condition and the need for prompt and appropriate intervention, if not already being instituted.

H/O sepsis secondary to pneumonia. treated with 4.5 L sodium chloride 0.9%. blood pressure was 82/40 mmHg. In attempting to restore the blood pressure, what is the most appropriate intravenous therapy?

**>> noradrenaline (norepinephrine)**

Ref: www.mrcpuk.org/ Acute Medicine Specialty Certificate Examination/ sample questions

# Respiratory Infections

## Respiratory pathogens

The table below lists the more common respiratory pathogens:

| Pathogen | Associated condition |
|---|---|
| **Respiratory syncytial virus** | Bronchiolitis |
| **Parainfluenza virus** | Croup |
| **Rhinovirus** | **Common cold** |
| **Influenza virus** | Flu |
| **Streptococcus pneumoniae** | The most common cause of **community-acquired pneumonia** |
| **Haemophilus influenzae** | Community-acquired pneumonia<br>Most common cause of **bronchiectasis exacerbations**<br>**Acute epiglottitis** |
| **Staphylococcus aureus** | Pneumonia, particularly **following influenza** |
| **Mycoplasma pneumoniae** | Atypical pneumonia<br><br>Flu-like symptoms classically precede a dry cough. Complications include haemolytic anaemia and erythema multiforme |
| **Legionella pneumophilia** | Atypical pneumonia<br><br>Classically spread by air-conditioning systems, causes dry cough. Lymphopenia, deranged liver function tests and hyponatraemia may be seen |
| **Pneumocystis jiroveci** | Common cause of pneumonia in HIV patients. Typically patients have few chest signs and develop exertional dyspnoea |
| **Mycobacterium tuberculosis** | Causes tuberculosis. A wide range of presentations from asymptomatic to disseminated disease are possible. Cough, night sweats and weight loss may be seen |

# Acute epiglottitis

- Acute epiglottitis is rare but serious infection caused by **Haemophilus influenzae type B.**
- Prompt recognition and treatment is essential as airway obstruction may develop.
- Epiglottitis generally occurs in **young children** between the ages of 2 and 6 years.
- The incidence of epiglottitis has decreased since the introduction of the Hib vaccine.

## Features

- Rapid onset
- Unwell, febrile and toxic child
- Stridor
- **Drooling of saliva**
- 'tripod' position: the patient finds it easier to breathe if they are leaning forward and extending their neck in a seated position

## Diagnosis

is made by direct visualization (only by senior/airway trained staff, see below). However, x-rays may be done, particularly if there is concern about a foreign body:

- a lateral view in acute epiglottis will show swelling of the epiglottis - the 'thumb sign'
- in contrast, a posterior-anterior view in croup will show subglottic narrowing, commonly called the 'steeple sign'

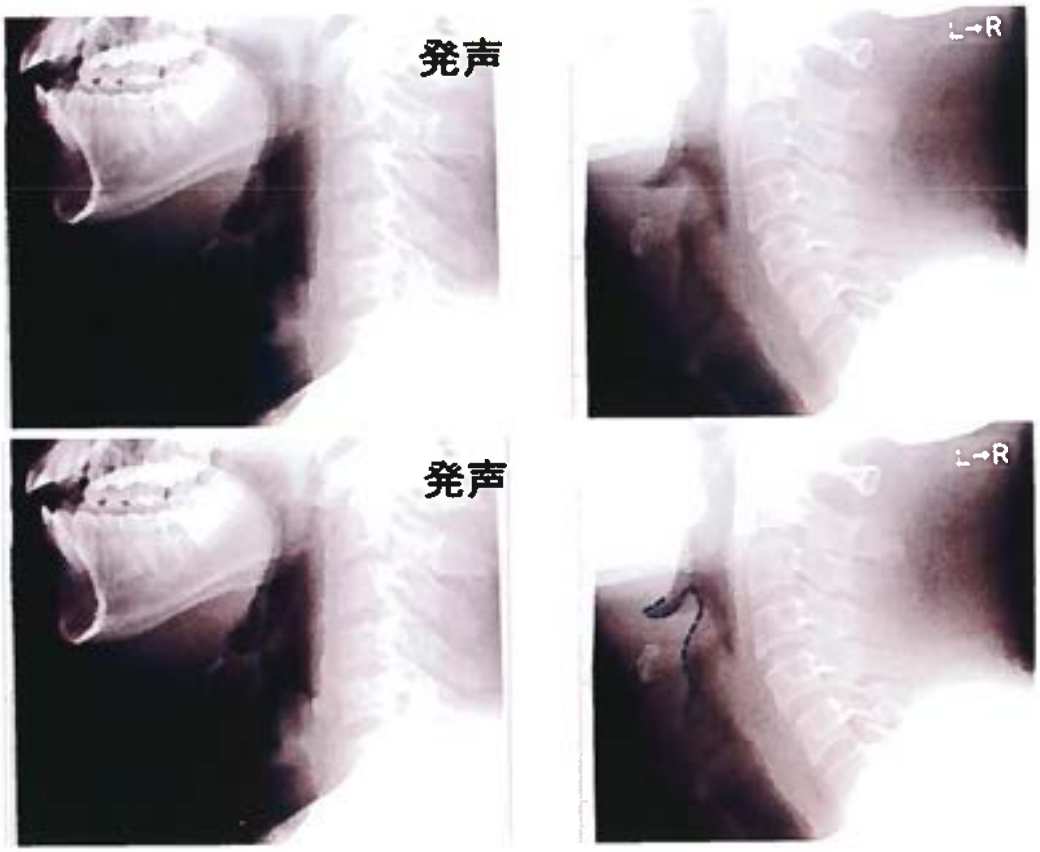



Image showing a normal epiglottis on the left and an inflamed one on the right. Annotated in blue in the bottom two images.

## Management

- immediate senior involvement, including those able to provide emergency airway support (e.g. anaesthetics, ENT)
  - endotracheal intubation may be necessary to protect the airway
- if suspected do NOT examine the throat due to the risk of acute airway obstruction
  - the diagnosis is made by direct visualisation but this should only be done by senior staff who are able to intubate if necessary
- oxygen
- intravenous antibiotics

# Croup

Croup is a form of upper respiratory tract infection seen in infants and toddlers. It is characterized by stridor which is caused by a combination of laryngeal oedema and secretions. Parainfluenza viruses account for the majority of cases.

## Epidemiology

- peak incidence at 6 months - 3 years
- more common in autumn

## Features

- stridor
- barking cough (worse at night)
- fever
- coryzal symptoms

**Clinical Knowledge Summaries (CKS) suggest using the following criteria to grade the severity:**

| Mild | Moderate | Severe |
|---|---|---|
| • Occasional barking cough<br>• No audible stridor at rest<br>• No or mild suprasternal and/or intercostal recession<br>• The child is happy and is prepared to eat, drink, and play | • Frequent barking cough<br>• Easily audible stridor at rest<br>• Suprasternal and sternal wall retraction at rest<br>• No or little distress or agitation<br>• The child can be placated and is interested in its surroundings | • Frequent barking cough<br>• Prominent inspiratory (and occasionally, expiratory) stridor at rest<br>• Marked sternal wall retractions<br>• Significant distress and agitation, or lethargy or restlessness (a sign of hypoxaemia)<br>• Tachycardia occurs with more severe obstructive symptoms and hypoxaemia |

CKS suggest admitting any child with moderate or severe croup. Other features which should prompt admission include:

- < 6 months of age
- known upper airway abnormalities (e.g. Laryngomalacia, Down's syndrome)
- uncertainty about diagnosis (important differentials include acute epiglottitis, bacterial tracheitis, peritonsillar abscess and foreign body inhalation)

### Investigations

- the vast majority of children are diagnosed clinically
- however, if a chest x-ray is done:
  - a posterior-anterior view will show subglottic narrowing, commonly called the 'steeple sign'
  - in contrast, a lateral view in acute epiglottis will show swelling of the epiglottis - the 'thumb sign'

### Management

- CKS recommend giving a single dose of oral dexamethasone (0.15mg/kg) to all children regardless of severity
- prednisolone is an alternative if dexamethasone is not available

### Emergency treatment

- high-flow oxygen
- nebulized adrenaline

## Diphtheria

Diphtheria is caused by the Gram-positive bacterium Corynebacterium diphtheriae

### Pathophysiology

- releases an exotoxin encoded by a β-prophage
- exotoxin inhibits protein synthesis by catalyzing ADP-ribosylation of elongation factor EF-2
- Diphtheria toxin commonly causes a 'diphtheric membrane' on tonsils caused by necrotic mucosal cells. Systemic distribution may produce necrosis of myocardial, neural and renal tissue

### Possible presentations

- recent visitors to Eastern Europe/Russia/Asia
- sore throat with a 'diphtheric membrane' - grey, pseudomembrane on the posterior pharyngeal wall
- bulky cervical lymphadenopathy
  - may result in a 'bull neck' appearanace

- neuritis e.g. cranial nerves
- **heart block**

### Investigations

- culture of throat swab: uses tellurite agar or Loeffler's media

### Management

- intramuscular penicillin
- diphtheria antitoxin

### Complications

- The toxin affects the myocardium, nervous and adrenal tissues.

## H1N1 influenza pandemic

- The H1N1 virus is a subtype of the influenza A virus
- **the most common cause of flu in humans.**
- The 2009 pandemic was caused by a new strain of the H1N1 virus.
- Only influenza type A viruses are known to have caused **pan**demics.
- Influenza A and B viruses circulate and cause outbreaks and **epi**demics.
- incubation period is about 2 days.

### The following groups are particularly at risk:

- patients with chronic illnesses and those on immunosuppressants
- pregnant women
- young children under 5 years old

### Features

The majority of symptoms are typical of those seen in a flu-like illness:

- fever greater than 38°C
- myalgia
- lethargy
- headache
- rhinitis
- sore throat
- cough
- diarrhoea and vomiting

**A minority of patients may go on to develop an acute respiratory distress syndrome which may require ventilatory support.**

## Treatment

**There are two main treatments currently available:**

**Oseltamivir (Tamiflu)**

- oral medication
- a neuraminidase inhibitor which prevents new viral particles from being released by infected cells
- common side-effects include nausea, vomiting, diarrhoea and headaches

**Zanamivir (Relenza)**

- inhaled medication*
- also a neuraminidase inhibitor
- may induce bronchospasm in asthmatics

Intravenous preparations are available for patients who are acutely unwell

# Legionella

Legionnaire's disease is caused by the intracellular bacterium *Legionella pneumophilia*.
It typically colonizes water tanks and hence questions may hint at air-conditioning systems or foreign holidays.
Person-to-person transmission is not seen

## Features

- flu-like symptoms including fever (present in > 95% of patients)
- dry cough
- **relative bradycardia**
- **confusion**
- **lymphopaenia**
- **hyponatraemia**
- **deranged liver function tests**
- pleural effusion: seen in around 30% of patients

## Diagnosis

- **urinary antigen**

## Management

- **treat with erythromycin/clarithromycin**

| Legionella pneumonia | | Mycoplasma pneumonia |
|---|---|---|
| | Atypical pneumonia | Haemolytic anaemia / ITP |
| Lymphopenia | Flu-like symptoms | Erythema multiforme |
| Hyponatraemia | Dry cough | Encephalitis / GBS |
| Diagnosis: urinary antigen | Deranged LFTs | Peri / myocarditis |
| | Treat with macrolide (e.g. erythromycin) | Diagnosis: serology |

Comparison of Legionella and Mycoplasma pneumonia

Chest x-ray features of legionella pnuemonia are non-specific but includes a mid-to-lower zone predominance of patchy consolidation. Pleural effusions are seen in around 30%.

# Mycoplasma pneumoniae

Mycoplasma pneumoniae is a cause of atypical pneumonia which often affects younger patients. It is associated with a number of characteristic complications such as erythema multiforme and cold autoimmune haemolytic anaemia. Epidemics of Mycoplasma pneumoniae classically occur every 4 years. It is important to recognise atypical pneumonia as it may not respond to penicillins or cephalosporins due to it lacking a peptidoglycan cell wall.

## Features

- the disease typically has a prolonged and gradual onset
- flu-like symptoms classically precede a dry cough
- bilateral consolidation on x-ray
- complications may occur as below

## Complications

- **cold agglutins (IgM):** may cause an **haemolytic anaemia,** thrombocytopenia
- **erythema multiforme,** erythema nodosum
- meningoencephalitis, Guillain-Barre syndrome and other immune-mediated neurological diseases
- **bullous myringitis:** painful vesicles on the tympanic membrane
- pericarditis/myocarditis
- gastrointestinal: hepatitis, pancreatitis
- renal: acute glomerulonephritis

## Investigations

- diagnosis is generally by Mycoplasma **serology**
- **positive cold agglutination test**

## Management

**doxycycline or a macrolide** (e.g. erythromycin/clarithromycin

# Skin and Soft Tissue Infections

## Cellulitis

Cellulitis is a term used to describe an inflammation of the skin and subcutaneous tissues, typically due to infection by **Streptococcus pyogenes** or **Staphylococcus aureus.**

### Features:

- Commonly occurs on the **shins**
- Erythema, pain, swelling
- There may be some associated systemic upset such as fever

The diagnosis of cellulitis is clinical. No further investigations are required in primary care. Bloods and blood cultures may be requested if the patient is admitted and septicemia is suspected.

### Criteria for admission

NICE Clinical Knowledge Summaries recommend we use the Eron classification to guide how we manage patients with cellulitis:

| Class | Features |
|---|---|
| I | There are no signs of systemic toxicity and the person has no uncontrolled co-morbidities |
| II | The person is either systemically unwell or systemically well but with a co-morbidity (for example peripheral arterial disease, chronic venous insufficiency, or morbid obesity) which may complicate or delay resolution of infection |
| III | The person has significant systemic upset such as acute confusion, tachycardia, tachypnoea, hypotension, or unstable co-morbidities that may interfere with a response to treatment, or a limb-threatening infection due to vascular compromize |
| IV | The person has sepsis syndrome or a severe life-threatening infection such as necrotizing fasciitis |

They recommend the following that we admit for intravenous antibiotics the **following patients:**

- Has Eron Class III or Class IV cellulitis.
- Has severe or rapidly deteriorating cellulitis (for example extensive areas of skin).
- Is very young (under 1 year of age) or frail.

- Is immunocompromized.
- Has significant lymphoedema.
- Has facial cellulitis (unless very mild) or periorbital cellulitis.

**The following is recommend regarding Eron Class II cellulitis:**

- Admission may not be necessary if the facilities and expertise are available in the community to give intravenous antibiotics and monitor the person - check local guidelines.
- Other patients can be treated with oral antibiotics.

## Management

- The BNF recommends **flucloxacillin as first-line treatment for mild/moderate cellulitis.**
- Clarithromycin, erythromycin (in pregnancy) or doxycycline is recommended in patients allergic to penicillin.
- NICE recommend that patients with severe cellulitis should be offered co-amoxiclav, cefuroxime, clindamycin or ceftriaxone.

**EX: Penicillin** is the antibiotic of choice for group A streptococcal infections. The BNF suggests **stopping flucloxacillin if streptococcal infection is confirmed by swab in patients with cellulitis, due to the high sensitivity**. This should be balanced however with the variable absorption of phenoxymethyl penicillin.

# Necrotising fasciitis

Necrotising fasciitis is a **surgical emergency** that is difficult to recognise in the early stages.

**It can be classified according to the causative organism:**

- **Type 1** is caused by **mixed aerobes and anaerobes** (often occurs post-surgery in diabetics).
- **Type 2** is caused by group A beta- haemolytic **Streptococcus pyogenes.**

## Risk factors

- skin factors: recent trauma, burns or soft tissue infections
- diabetes mellitus
  - the most common preexisting medical condition
  - particularly if the patient is treated with SGLT-2 inhibitors
- intravenous drug use
- immunosuppression

**The most commonly affected site is the perineum (Fournier's gangrene).**

## Features:

- acute onset
- pain, swelling, erythema at the affected site
  - often presents as **rapidly worsening cellulitis with pain out of keeping with physical features**
  - extremely tender over infected tissue with hypoaesthesia to light touch
  - skin necrosis and crepitus/gas gangrene are late signs
- fever and tachycardia may be absent or occur late in the presentation

## Management:

- **Urgent surgical debridement.**
- I.V antibiotics (**Clindamycin** and **benzyl penicillin**).

**Prognosis:** average mortality of 20%

**EX:** A 45-year-old man presents to the Emergency Department due to **severe pain** in the perineal area **over the past 6 hours**. On examination the skin is cellulitic, **extremely tender** and **haemorrhagic bullae** are seen.
What is the most appropriate management? >>> Urgent surgical debridement.

Surgical referral is the single most important step in the management of necrotising fasciitis. There has been little change in the mortality of necrotising fasciitis since the introduction of antibiotics.

# Bone and Joints Infections

## Septic arthritis

### Overview:

- Most common organism overall is **Staphylococcus aureus.**
- In young adults who are sexually active **Neisseria gonorrhoeae** should also be considered.
- **Salmonella infection** in sickle cell disease patients.

### Management:

- Synovial fluid should be obtained before starting treatment
- Intravenous antibiotics which cover Gram-positive cocci are indicated. The BNF currently recommends **flucloxacillin** or clindamycin if penicillin allergic.
- Antibiotic treatment is normally be given for several weeks (BNF states **6-12 weeks**).
- Needle aspiration should be used to decompress the joint.
- Surgical drainage may be needed if frequent needle aspiration is required.

Septic arthritis >>> IV flucloxacillin

## Osteomyelitis

Osteomyelitis describes an infection of the bone.
***Staph. Aureus*** is the most common cause, except in patients with **sickle-cell** anaemia where **Salmonella** species predominate.

### Predisposing conditions:

- **DM**
- Sickle cell anaemia
- I.V drug user
- Immunosuppression due to either medication or HIV
- Alcohol excess

### Investigations:

- **MRI** is the imaging modality of choice, with **a sensitivity of 90-100%.**

### Management:

- Flucloxacillin for 6 weeks
- Clindamycin if penicillin-allergic

# Central Nervous system Infections

## Meningitis

### Causes

**0 - 3 months:**

- Group B Streptococcus (most common cause in neonates)
- E. coli
- Listeria monocytogenes

**3 months - 6 years:**

- Neisseria meningitidis
- Streptococcus pneumoniae
- Haemophilus influenzae

**6 years - 60 years:**

- **Neisseria meningitidis**
- **Streptococcus pneumoniae**
- **Listeria monocytogenes**

**Immunosuppressed:**

- **Listeria monocytogenes**

Risk factors for **listeria** meningitis include **older** age and **immunosuppression (e.g. prolonged steroid usage for temporal arteritis)**.

Meningitis following **neurosurgical procedures** such as V-P shunt operation for hydrocephalus tends to involve a different groups of organisms to normally acquired meningitis. **75%** of all infections involving **VPS** are caused by **staphylococcus epidermis,** next commonest is **staphylococcus aureus** and then **Gram negative bacilli** such as E-Coli, Proteus or Klebsiella.

**Normal CSF:**

| | |
|---|---|
| Opening pressure | 5-18 **cm H2O** |
| Glucose | 3.3-4.4 mmol |
| Protein | 0.15-0.45 g/l |
| WBC | < 5/ml |

### Investigations

**Investigations suggested by NICE:**

- CBC, CRP
- Coagulation screen
- Blood culture
- Whole-blood PCR

- Blood glucose
- ABG
- Lumbar puncture **if** no signs of raised intracranial pressure.

## CSF analysis

The characteristic cerebrospinal fluid (CSF) findings in meningitis:

| | Bacterial | Viral | Tuberculosis |
|---|---|---|---|
| Appearance | Cloudy | Clear/cloudy | Fibrin web |
| Glucose | Low (< 1/2 plasma) | Normal | Low (< 1/2 plasma) |
| Protein | High (> 1 g/l) | Normal/raised | High (> 1 g/l) |
| White cells | 10 - 5,000 polymorphs/mm³ | 15 - 1,000 lymphocytes/mm³ | 10 - 1,000 lymphocytes/mm³ |

**NB**: The Ziehl-Neelsen stain is only 20% sensitive in the detection of **tuberculous meningitis** and therefore **PCR** is usually used (sensitivity = **75%**).

**N.B:** Mumps is unusual in being associated with a low glucose level in a prop
**N.B:** A low glucose may also be seen in herpes encephalitis
ortion of cases.

**NB:** A clinical meningitis with an **elevated CSF pressure**, **slightly elevated protein** and **lymphocytosis** is likely to be of viral aetiology, particularly in **young** previously **fit** individual.
**EX**: Young female returns from a trip to France with 4-day history of headache, vomiting, fever and neck stiffness >>> **viral meningitis.**

## Management:

- All patients should be transferred to hospital urgently.
- If patients are in a pre-hospital setting (for example a GP surgery) and meningococcal disease is suspected then **intramuscular benzyl penicillin** may be given, as long as this doesn't delay transit to hospital.

Penicillin may cause an **eosinophilic drug reaction**, therefore may be after 3 days of treatment with it the patient develop spikes of new fever with increased eosinophil count in peripheral blood >>> **Stop penicillin and replace with cephalosporin (cefotaxime).**

Indeed most centres use a cephalosporin as first line therapy because of the small risk of meningococcal resistance to penicillin:

- **< 55 years**: **Cefotaxime** 2 gm/6hrs IVI.
- **>55 years**: **Cefotaxime** as above + **Ampicillin** 2 gm/4hrs IVI (for Listeria).

**BNF recommendations on antibiotics:**

| Scenario | BNF recommendation |
|---|---|
| Initial empirical therapy aged < 3 months. | Cefotaxime IV + amoxicillin |
| Initial empirical therapy aged 3 months - 50 years. | Cefotaxime IV |
| **Initial empirical therapy aged > 50 years** | **Cefotaxime IV + amoxicillin** |
| Meningococcal meningitis | Benzylpenicillin IV or cefotaxime |
| Pneumococcal meningitis | Cefotaxime IV |
| Meningitis caused by Haemophilus influenzae | Cefotaxime IV |
| Meningitis caused by Listeria | Amoxicillin IV + gentamicin |

**Intravenous dexamethasone** should also be given to reduce the risk of neurological sequelae, but the BNF advise to withhold if:

- septic shock
- meningococcal septicaemia
- immunocompromised
- meningitis following surgery

If the patient has a history of immediate hypersensitivity reaction to penicillin or to cephalosporins the BNF recommends using **chloramphenicol**.

## Management of contacts:

- Prophylaxis needs to be offered to household and close contacts of patients affected with meningococcal meningitis.
- **Prophylaxis medication:**
  - **Oral Rifampicin (300 mg: 2 x 2 x 2)** or
  - **Ciprofloxacin 500 mg single oral dose or**
  - **Ceftriaxone single IM** dose may be used and ttt of choice in pregnant women.
- The Health Protection Agency (HPA) guidelines now state that whilst either may be used **ciprofloxacin is the drug of choice** as it is widely available and only requires one dose.
- The risk is highest in the first 7 days but persists for at least 4 weeks.
- **Meningococcal vaccination** should be offered to close contacts when serotype results are available, including booster doses to those who had the vaccine in infancy.
- for pneumococcal meningitis, no prophylaxis is generally needed. There are however exceptions to this. If a cluster of cases of pneumococcal meningitis occur the HPA have a protocol for offering close contacts antibiotic prophylaxis.

**MRCPUK part 1 exam:** A 57-year-old female presents with headache, fever, neck stiffness with a positive Kernig's sign. CSF culture: Gram positive bacilli. *What is the most likely causative organism?* ***>> Listeria monocytogenes***

**MRCPUK part 1 exam:** A 47-year-old lady with Feature of fever, headache and nuchal rigidity. Lumbar puncture reveals: Appearance: Cloudy. Glucose:1.7 mmol/l. Protein:1.9 g/l. White cells: 900 / mm³ (90% polymorphs). What is the most likely infective agent?

**>> *Streptococcus pneumoniae***

- (CSF >> results bacterial meningitis (low glucose, high protein, high polymorphs). In this age group Streptococcus pneumoniae and Neisseria meningitidis are the most common causes of bacterial meningitis)

**MRCPUK part 1 exam:** A diagnosis of pneumococcal meningitis is made. There are no other reports of meningitis in the local area over the past 4 weeks. How should the close contacts of this boy be managed?

**>> No action is needed (unless cluster of cases develop)**

**MRCPUK part 1 exam:** A 23-year-old man is admitted with purpuric rash, pyrexia and confusion. His GP had given him intramuscular benzylpenicillin. Which one of the following investigations is most likely to **reveal the diagnosis?** **>> Blood PCR for meningococcus**

- (The blood cultures are likely to be negative as antibiotics have already been given. PCR has a sensitivity of over 90%)

## Meningococcal septicaemia

Meningococcal septicaemia is a frightening condition for patients, parents and doctors.

It is associated with a high morbidity and mortality unless treated early.

The meningococcal disease is the leading infectious cause of death in early childhood.

A high index of suspicion is therefore needed.

### Presentation of meningococcal disease:

- 15% - meningitis.
- 25% - septicaemia.
- **60%** - a **combination** of **meningitis** and **septicaemia.**

### Investigations:

- **Blood cultures.**
- **Blood PCR** (It has a sensitivity of over 90%) (It is used if antibiotic was already started).
- Lumbar puncture is usually **contraindicated.**

- full blood count and clotting to assess for disseminated intravascular coagulation

### Management

- **the most important initial step >> administration of intravenous antibiotics (cefotaxime) is the greatest priority, regardless of whether cultures have been sent.**

# Urinary tract infection

## Urinary tract infection (UTI) in adults: management

### 1) Lower urinary tract infections in non-pregnant women:

- Local antibiotic guidelines should be followed if available.
- SIGN guidelines recommend trimethoprim or nitrofurantoin for 3 days.

**2) Pregnant women with symptomatic bacteriuria** should be treated with an antibiotic for 7 days. A urine culture should be sent.

### 3) For asymptomatic pregnant women:

- A urine culture should be performed routinely at the first antenatal visit.
- If positive, a second urine culture should be sent to confirm the presence of bacteriuria.
- SIGN recommend **to treat asymptomatic bacteriuria** detected during **pregnancy** with an **antibiotic**.
- A 7 day course of antibiotics should be given.
- A further urine culture should be sent following completion of treatment as a test of cure.

So, Pregnant women with symptomatic or asymptomatic UTI >>> treatment: **R/Amoxycillin for 7 days. (500 mg x 3 x 7).**

### 4) For patients with sign of acute pyelonephritis:

- Hospital admission should be considered.
- Local antibiotic guidelines should be followed if available.
- The BNF currently recommends a broad-spectrum **cephalosporin** or a **quinolone** for 10-14 days.

**Ciprofloxacin** has still been recommended as **first** line therapy by SIGN for symptoms of **upper** UTI.
**Trimethoprim** resistance is apparently as high as 40% but it is still recommended as a 3 day course for uncomplicated **lower** UTI.

# Zoonotic, Ectoparasites Infections and protozoans

## Leptospirosis (Weil's disease)

Also known as **Weil's disease** (the term Weil's disease is sometimes reserved for the most severe 10% of cases that are associated with jaundice.

Leptospirosis is commonly seen in questions referring to **sewage** workers, **fish farm, farmers,** vets or people who work in abattoir.
It is caused by the spirochaete Leptospira interrogans (serogroup L icterohaemorrhagiae), classically being spread by contact with **infected rat urine.**

Weil's disease should always be considered in high-risk patients with **hepatorenal** failure.

### Features:

**the early phase is due to bacteraemia and lasts around a week**

- **Fever.**
- **Flu-like symptoms. (WITHOUT PRODUCTIVE COUGH)**
- **Renal failure** (seen in **50%** of patients). **↓UOP.**
- **Jaundice** (Liver failure is seen in **only 10%** of patients with leptospirosis).
- **Sub-conjunctival haemorrhage**
- **Thrombocytopenia.**
- **↑ CPK**
- Headache, may herald the onset of meningitis (**meningism**).

### Investigation

- **serology**: antibodies to *Leptospira* develop after about 7 days
- PCR
- culture
  - growth may take several weeks so limits usefulness in diagnosis
  - blood and CSF samples are generally positive for the first 10 days
  - urine cultures become positive during the second week of illness

### Management:

- High-dose **benzylpenicillin IV** or IV Cephalosporin or **doxycycline**

Leptospirosis give **meningism** picture with **treatment** by **Doxycycline**

# Brucellosis

Brucellosis is a zoonosis more common in the Middle East and in farmers.
It is a small slow-growing intracellular organism which histopathologically causes a chronic granulomatous disease.

The Brucella species are small **Gram negative aerobic coccobacilli**

Transmission to humans occurs after occupational exposure or through ingestion of contaminated food products, especially unpasteurised milk products.

### Four major species cause infection in humans:

1) B. melitensis (sheep),
2) B. abortus (cattle),
3) B. canis
4) B. suis (pigs).

Brucellosis has an incubation period 2 - 6 weeks.

### Transmission is through:

- ingestion of unpasteurised milk
- inhalation of infectious aerosols
- direct inoculation through cuts, and
- conjunctival inoculation

## Features:

- Non-specific: fever, malaise, paradoxical bradycardia
- **Hepatosplenomegaly**
- **Sacroiliitis**: spinal tenderness may be seen in up to 55% of cases.
- **Leukopenia** and **thrombocytopenia** are often seen.
- Complications: osteomyelitis, infective endocarditis, meningo-encephalitis, orchitis.

## Diagnosis:

- **Bone marrow aspiration and culture** is the **gold standard** for diagnosis of brucellosis.
- **Brucella serology** is the best test for diagnosis.
- Blood culture is only positive in 15-70% of cases: **Gm negative coccobacilli.**
- The Rose Bengal plate test can be used for screening but other tests are required to confirm the diagnosis.

## Management: **doxycycline** and **streptomycin**

## Anthrax

Anthrax is caused by Bacillus anthracis, a **Gram-positive rod**.
It is spread by infected carcasses.
It is also known as Wool sorters' disease.

**Bacillus anthracis produces a tripartite protein toxin:**

- Protective antigen
- **Oedema factor**: a bacterial **adenylate cyclase** which **increases cAMP**
- Lethal factor: toxic to macrophages

### Features:

- Causes **painless black eschar** (cutaneous 'malignant pustule', but **NO pus**).
- Typically, painless and non-tender.
- May cause **marked oedema**.
- Anthrax can cause gastrointestinal bleeding.

### Management:

- The initial management of **cutaneous anthrax** is **ciprofloxacin.**
- Further ttt is based on microbiological investigations and expert advice.
- **Without antibiotics mortality** is of the order of **20%**, but **with antibiotics**, mortality is **low**, which contrasts with pulmonary anthrax.

## Animal bites

The majority of bites seen in everyday practice involve **dogs** and **cats**.
These are generally polymicrobial but **the most common isolated organism** is **Pasteurella multocida.**

### Management:

- Cleanse wound
- Current BNF recommendation is **co-amoxiclav.**
- If penicillin-allergic then **doxycycline + metronidazole** is recommended.

**MRCPUK part 1 exam: H/O a dog bite to right hand. What is the most appropriate antibiotic therapy? >>> Co-amoxiclav**

**MRCPUK part 1 exam: A patient has been bitten by his dog that morning. the wound looks clean as he has washed it well. He is penicillin allergic. Which antibiotic therapy is suitable?**
**>>> Metronidazole and doxycycline in combination**

## Cat scratch disease

It is generally caused by the Gram negative rod **Bartonella henselae.**

### Features:

- **Fever**
- **History of a cat scratch**
- **Regional lymphadenopathy**
- Headache, malaise

### Treatment

- Mild or moderate cases: azithromycin (5-day course) to decrease lymphadenopathy and the duration of illness
- In the case of persistent and/or disseminated disease (e.g., bacillary angiomatosis): erythromycin OR doxycycline
- In the case of CNS involvement or endocarditis: rifampicin PLUS either erythromycin OR doxycycline

## Scabies

Scabies is caused by the mite Sarcoptes scabiei and is spread by prolonged skin contact. It typically affects children and young adults.

Scabies should be suspected in any sexually active young person who presents with generalised pruritus without any specific signs.

### Pathophysiology

- The scabies mite burrows into the skin, laying its eggs in the stratum corneum.
- The intense pruritus associated with scabies is due to a **delayed type IV hypersensitivity reaction** to mites/eggs which occurs about 30 days after the initial infection.

### Features:

- Widespread pruritus.
- **Linear burrows on the side of fingers, interdigital webs and flexor aspects of the wrist.**
- In infants the face and scalp may also be affected.
- Secondary features are seen due to scratching: excoriation, infection.

**Diagnosis**: by demonstrating Sarcoptes scabiei on **skin scrapings**.

## Management:

- Permethrin 5% is first-line
- Malathion 0.5% is second-line
- Give appropriate guidance on use (see below)
- **Pruritus persists for up to 4-6 weeks post eradication.** (i.e. It is normal for pruritus to persist for up to 4-6 weeks post eradication and it needs no further ttt)

**Patient guidance on treatment** (from Clinical Knowledge Summaries):

- Avoid close physical contact with others until treatment is complete.
- **All household and close physical contacts should be treated at the same time, even if asymptomatic.**
- Launder, iron or tumble dry clothing, bedding, towels, etc., on the first day of treatment to kill off mites.

**Patients should be given the following instructions**

- The BNF advises to apply the insecticide to **all areas**, including the face and scalp, contrary to the manufacturer's recommendation. Patients should be given the following instructions:
- Apply the insecticide cream or liquid to cool, dry skin.
- Pay close attention to areas between fingers and toes, under nails, armpit area, creases of the skin such as at the wrist and elbow.
- **Allow to dry** and **leave on the skin for 8-12 hours for Permethrin**, or for 24 hours for Malathion, before washing off.
- Reapply if insecticide is removed during the treatment period, e.g. If wash hands, change nappy, etc.
- **Repeat treatment 7 days later.**

## Crusted (Norwegian) scabies:

- **Crusted scabies** is seen in patients with **suppressed immunity, especially HIV.**
- The crusted skin will be teeming with hundreds of thousands of organisms.
- **Ivermectin** is the treatment of choice and isolation is essential.

# Lyme disease (Borreliosis)

It is caused by at least 3 species of bacteria belonging to the genus Borrelia.

It is very common in Connecticut where it was given its name when it infected a large group of children in Lyme.

**Borrelia burgdorferi** sensu stricto is the main cause of Lyme disease in USA.

Whereas Borrelia afzelii and Borrelia garinii cause most European cases.

Around 20% of infections in the UK occur abroad, and **Austria** is a recognised location for Lyme infection.

**There are several phases to Lyme disease:**

- The **first** being initial headache and neck stiffness.
- The **second** phase normally occurs between 1 to 6 months after infection and presents as meningitis, multiple cranial or peripheral neuropathies, or an acute polyneuropathy resembling Guillain-Barré syndrome.
- Stage **three** of the disease occurs months to years after infection and presents as a chronic myelitis, encephalopathy or demyelinating disorder.

## Features:

- **Early:**
  1) **Erythema chronicum migrans** (small papule often at site of the **tick bite** which develops into a larger annular lesion with **clear centre**, **'bulls-eye'.** Occurs in **70%** of patients).
  2) Systemic features **(flu like illness, headache, lethargy, fever,** and **arthralgia).**
- **Later:**
  1) **CVS**: heart block, prolonged PR interval, myocarditis.
  2) **Neuro**: cranial nerve palsies **(facial Bell's palsy), meningitis.**
  3) **Joints**: **Polyarthritis.**

Lyme disease can **easily be confused** with **rheumatic fever** and **infective endocarditis.**

## Investigation:

- NICE recommend that Lyme disease can be diagnosed clinically if erythema migrans is present
  - erythema migrans is therefore an indication to start antibiotics
- enzyme-linked immunosorbent assay **(ELISA) antibodies to *Borrelia burgdorferi* are the first-line test**
  - if negative and Lyme disease is still suspected in people tested within 4 weeks from symptom onset, repeat the ELISA 4-6 weeks after the first ELISA test. If still suspected in people who

have had symptoms for 12 weeks or more then an immunoblot test should be done
  - **if positive or equivocal then an immunoblot test for Lyme disease should be done**

## Management:

- **Doxycycline for 2-3 weeks** if **early** disease, and it is the drug of choice for those above 8 years and non-pregnant females.
- **Amoxicillin** is an alternative if doxycycline is contraindicated (e.g. **pregnancy).**
- people with erythema migrans should be commenced on antibiotic without the need for further tests
- **Ceftriaxone 2gm IV daily** if **disseminated** disease.
- **Jarisch-Herxheimer reaction** is sometimes seen after initiating therapy: fever, rash, tachycardia after first dose of antibiotic (more commonly seen in syphilis, another spirochaetal disease).

**MRCPUK part 1 exam: H/O returning from a camping holiday in the New Forest. C/O lethargy, arthralgia, rash consistent with erythema chronicum migrans. What is the most appropriate test to perform given the likely diagnosis?**

**>>> ELISA test for antibodies to *Borrelia burgdorferi***

# Toxoplasmosis

- **Toxoplasma gondii** is a **protozoa** which infects the body via the GI tract, lung or broken skin.
- Its oocysts release trophozoites which migrate widely around the body including to the eye, brain and muscle.
- The usual animal reservoir is the **cat**, although others such as **rats** carry the disease.

### Immunocompotent patients

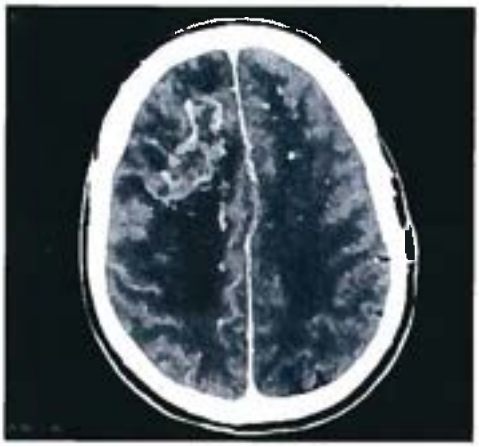
Most infections are asymptomatic. Symptomatic patients usually have a self-limiting infection, often having clinical features **resembling infectious mononucleosis** (fever, malaise, lymphadenopathy).
Other less common manifestations include meningoencephalitis and myocarditis.

## Serology is the investigation of choice.

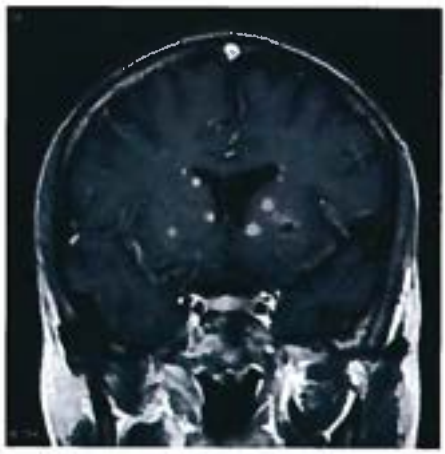
### HIV/immunosuppressed patients

Cerebral toxoplasmosis accounts for around 50% of cerebral lesions in patients with HIV

- constitutional symptoms, headache, confusion, drowsiness
- CT: usually single or multiple ring-enhancing lesions, mass effect may be seen
- management: **pyrimethamine plus sulphadiazine** for at least 6 weeks



Cerebral toxoplasmosis: CT scan with contrast showing multiple ring enhancing lesions



Cerebral toxoplasmosis: MRI (T1 C+) demonstrates multiple small peripherally enhancing nodules located predominantly in the basal ganglia as well as the central portions of the cerebellar hemispheres. Only a small amount of surrounding oedema is present.

**Immunosuppressed patients may also develop a chorioretinitis secondary to toxoplasmosis.**

## Congenital toxoplasmosis

Congenital toxoplasmosis is due to transplacental spread from the mother. It causes a variety of effects to the unborn child including

- neurological damage
  - **cerebral calcification**

  - hydrocephalus
  - **chorioretinitis**
- ophthalmic damage
  - retinopathy
  - cataracts

## Treatment

- **Pyrimethamine + sulphadiazine** for **at least 6 weeks**.
- **No treatment is usually required unless the patient has a severe infection or is immunosuppressed.**

**exam: HIV positive man is admitted with right-sided hemiplegia. CT scan shows multiple ring enhancing lesions. A diagnosis of cerebral toxoplasmosis is suspected. What is the most suitable management?**
**>> Pyrimethamine and sulphadiazine**

**At which CD4 count should prophylaxis against toxoplasmosis begin? >> <100 cells/μL** (with trimethoprim-sulfamethoxazole). although prophylaxis for toxoplasmosis is not required until the CD4 count is <100 cells/microL, the patient will be covered at a CD4 count <200 cells/microL when prophylaxis against *P. jiroveci* is instituted.

**What is risk of transmission of HIV to a health care worker after percutaneous exposure?**

- **0.3% with** no prophylaxis.
  the risk is reduced by ~80% when post exposure prophylaxis is administered.

**HIV- white lesion in oral mucosa**

- **Oral hairy leukoplakia** are white oral lesions **caused by the Epstein-Barr virus**.
- a condition seen in HIV-infected patients with a CD4 count between 200 and 500/$mm^3$.
  Unlike oral candidiasis (thrush), these lesions **cannot be scraped off** the tongue and buccal mucosa.

## Cryptosporidiosis

Cryptosporidiosis is the commonest protozoal cause of diarrhoea in the UK. Two species, *Cryptosporidium hominis* and *Cryptosporidium parvum* account for the majority cases.

Cryptosporidiosis is more common in immunocompromised patients (e.g., HIV) and young children.

### Features

- watery diarrhea
- abdominal cramps
- fever
- in immunocompromised patients, the entire gastrointestinal tract may be affected resulting in complications such as sclerosing cholangitis and pancreatitis

**Diagnosis:** **stool:** **modified Ziehl-Neelsen stain** (acid-fast stain) of the stool may reveal the characteristic red cysts of Cryptosporidium

### Management

- is largely supportive for immunocompetent patients
- if the patient has HIV and is not on antiretroviral therapy then this should be started and often will be enough to resolve the infection
- **nitazoxanide** may be used for immunocompromised patients
- rifaximin is also sometimes used for immunocompromised patients/patients with severe disease

## Strongyloides stercoralis

Strongyloides stercoralis is a human parasitic nematode worm.
The larvae are present in soil and gain access to the body by **penetrating the skin.** Infection with *Strongyloides stercoralis* causes strongyloidiasis.

### Features

- diarrhea
- abdominal pain/bloating
- papulovesicular lesions where the skin has been penetrated by infective larvae **e.g., soles of feet and buttocks**
- larva currens: pruritic, linear, urticarial rash
- if the larvae migrate to the lungs a pneumonitis similar to Loeffler's syndrome may be triggered

### Treatment

- **ivermectin** and albendazole are used

## Wuchereria bancrofti

- Parasitic filarial nematode
- Accounts for 90% of cases of filariasis
- Usually diagnosed by blood smears
- Usually transmitted by mosquitos
- Treatment is with diethylcarbamazin

## Cutaneous larva migrans

Cutaneous larva migrans is caused by the infection of the dog hookworm **Ancyclostoma braziliense.**
Man is an accidental dead-end host and so the larva is unable to migrate to the lungs and intestine.
The intensely itchy, 'creeping' serpiginous rash is a result of the subcutaneous migration of the frustrated larva.
**Management** is with albendazole or ivermectin.

Typical 'creeping' serpiginous rash of vutaneous larva migrans

# Virology

## DNA viruses

| Family | Structure | Envelope | Examples/importance |
|---|---|---|---|
| Herpesviruses | Double-stranded, linear | Enveloped | Herpes simplex virus, varicella-zoster virus, cytomegalovirus, Epstein-Barr virus |
| Hepadnavirus | Double-stranded, circular | Enveloped | Hepatitis B virus |
| Adenovirus | Double-stranded, linear | Naked | Common cold, conjunctivitis |
| Parvovirus | **Single-stranded**, linear | Naked | Parvovirus B19 |
| Papillomavirus | Double-stranded, circular | Naked | HPV |
| Poxvirus | Double-stranded, linear | Enveloped | Smallpox, molluscum contagiosum |
| Polyomavirus | Double-stranded, circular | Naked | JC virus (progressive multifocal leukoencephalopathy) |

Parvovirus is the only DNA virus that is not double-stranded

HHAPPPPy! - Hepadna; Herpes; Adeno; Pox; Parvo; Papilloma; Polyoma

## RNA viruses

| Family | Structure | Envelope | Capsid Symmetry | Examples |
|---|---|---|---|---|
| Reoviridae | **Double-stranded**, linear | Naked | Icosahedral | Reovirus, Rotavirus |
| Picornaviridae | Single-stranded +, linear | Naked | Icosahedral | Enterovirus, Rhinovirus, Poliovirus, Coxsackie |
| Caliciviridae | Single-stranded +, linear | Naked | Icosahedral | Norwalk virus |
| Togaviridae | Single-stranded +, linear | Enveloped | Icosahedral | Rubella virus |
| Arenaviridae | Single-stranded -, circular | Enveloped | Helical | Lymphocytic choriomeningitis virus |
| Flaviviridae | Single-stranded +, linear | Enveloped | Icosahedral | Dengue virus, Hepatitis C virus, Yellow fever virus |
| Orthomyxoviridae | Single-stranded -, linear | Enveloped | Helical | Influenzavirus A, Influenzavirus B, Influenzavirus C, |
| Paramyxoviridae | Single-stranded -, linear | Enveloped | Helical | Measles virus, Mumps virus, Respiratory syncytial virus |
| Bunyaviridae | Single-stranded -, circular | Enveloped | Helical | California encephalitis virus, Hantavirus |
| Rhabdoviridae | Single-stranded -, linear | Enveloped | Helical | Rabies virus |
| Filoviridae | Single-stranded -, linear | Enveloped | Helical | Ebola virus, Marburg virus |
| Coronaviridae | Single-stranded +, linear | Enveloped | Helical | Corona virus |
| Hepeviridae | Single-stranded +, linear | Naked | Icosahedral | Hepatitis E virus |

**RNA viruses memory aids:**

Reoviridae are the only double-stranded RNA viruses

- 'CALL PICO and FLAVA. There's a RETRO TOGA party with lots of CORONAs'

# Cytomegalovirus

Cytomegalovirus (CMV) is one of the herpes viruses.
It is thought that around 50% of people have been exposed to the CMV virus although it only usually causes disease in the immunocompromised, for example people with HIV or those on immunosuppressants following organ transplantation.

## Pathophysiology

- **infected cells have a 'Owl's eye' appearance due to intranuclear inclusion bodies.**

## Patterns of disease

### Congenital CMV infection

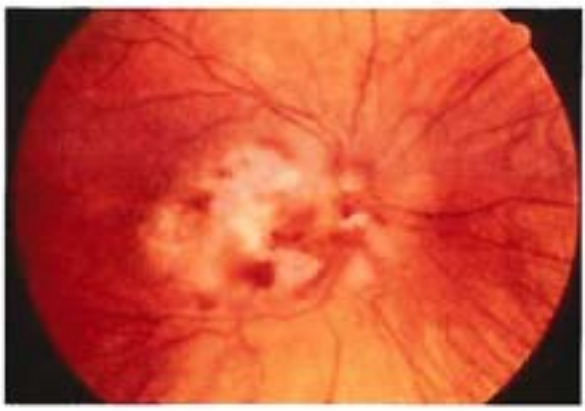
- features include growth retardation, pinpoint petechial 'blueberry muffin' skin lesions, microcephaly, sensorineural deafness, encephalitiis (seizures) and hepatosplenomegaly

### CMV mononucleosis

- infectious mononucelosis-like illness
- may develop in immunocompetent individuals

### CMV retinitis

- common in HIV patients with a low CD4 count (< 50)
- presents with visual impairment e.g. 'blurred vision'. Fundoscopy shows retinal haemorrhages and necrosis, often called 'pizza' retina
- IV ganciclovir is the treatment of choice



Fundus photograph showing CMV retinitis. Credit: National Eye Institute, National Institutes of Health

**CMV encephalopathy** :seen in patients with HIV who have low CD4 counts

**CMV pneumonitis**

**CMV colitis**

## Herpes simplex virus (HSV)

There are 2 strains of the HSV in humans: HSV-1 and HSV-2.
Whilst it was previously thought HSV-1 accounted for oral lesions (cold sores) and HSV-2 for genital herpes it is now known there is considerable overlap.

### Features:

- Primary infection: may present with a severe gingivostomatitis
- Cold sores
- **Painful** genital ulceration (localised tingling of the genitalia, and shooting pains).

### Management:

- Gingivostomatitis: oral acyclovir, chlorhexidine mouthwash.
- Cold sores: topical acyclovir although the evidence base for this is modest.
- Genital herpes:
  - **Oral acyclovir.**
  - If patient has **frequent exacerbations** more than **6 episodes yearly** may benefit from prophylactic ttt which consist of longer term **oral acyclovir for 3 months.**

### Pregnancy

- elective caesarean section at term is advised if a primary attack of herpes occurs during pregnancy at greater than 28 weeks gestation
- women with recurrent herpes who are pregnant should be treated with suppressive therapy and be advised that the risk of transmission to their baby is low

## Genital herpes

- Genital herpes is most commonly caused by **herpes simplex virus-2 (HSV).**
- **60%** of **primary** cases are **asymptomatic**.
- **Recurrent attacks** tend to be **shorter** and **less severe**.
- **Viral shedding (transmission)** can occur in the **absence** of lesions.
- **Antiviral** treatment **reduces** the severity of episodes but **is not curative**.
- Topical acyclovir is of **little** benefit.

**HSV II genital ulcers during pregnancy**: ttt **start Acyclovir immediately** at **any** trimester then if further active infection after week 36 then antiviral therapy and a **CS** may be recommended.

# Chickenpox

- Chickenpox is caused by primary infection with varicella zoster virus (VZV).
- Shingles is reactivation of dormant virus in dorsal root ganglion.
- **VZV** is the **MOST CONTAGIOUS ORGANISM.**

## Chickenpox is highly infectious:

- Spread via the **respiratory** route.
- Can be caught from someone with shingles.
- Infectivity = **4 days before rash, until 5 days after the rash first appeared.**
- Incubation period = 10-21 days.

## Clinical features (tend to be more severe in older children/adults):

- Fever initially
- Itchy, rash starting on **head/trunk** before spreading.
- Initially macular then papular then vesicular.
- Systemic upset is usually mild.

## Management is supportive:

- Keep cool, trim nails.
- Calamine lotion.
- School exclusion: current HPA advice is 5 days from start of skin eruption. They also state 'Traditionally children have been excluded until all lesions are crusted. However, **transmission has never been reported beyond the fifth day of the rash.'**
- Immunocompromised patients and newborns with peripartum exposure should receive **varicella zoster immunoglobulin (VZIG)**: see later.
- If chickenpox develops then **IV acyclovir** should be considered.

## Rare complications include:

- **Pneumonia.** (Chicken pox pneumonitis)
- Encephalitis (cerebellar involvement may be seen).
- DIC: Disseminated haemorrhagic chickenpox.
- Arthritis, nephritis and pancreatitis may very rarely be seen.

**N.B: Varicella pneumonia:** is the most common and serious complication of chickenpox infection in adults. Auscultation of the chest is often unremarkable, only occasional fine crackles bilaterally.
**Treatment** of Varicella pneumonia in normal adults >>> **IV acyclovir.**

**N.B: Varicella zoster virus IV immunoglobulin (VZV IVIG):** **only** recommended as **post exposure prophylaxis** i.e. used for **prevention** of varicella in at-**risk** groups (e.g. Immunocompromised, **pregnant** women, steroid user), rather than for treatment.

VZV IVIG should be used **within 3 days** of contact/exposure if possible and **not later than 10 days** after exposure. The **varicella antibody (IgG) status** should of course be assessed **firstly**.

So **firstly** check **Varicella IgG Ab**, if negative so **then VZV IVIG**.

Chest x-ray showing miliary opacities secondary to healed varicella pneumonia. Multiple tiny calcific miliary opacities noted throughout both lungs. These are of uniform size and dense suggesting calcification. There is no focal lung parenchymal mass or cavitating lesion seen. The appearances are characteristic for healed varicella pneumonia.

## Chickenpox exposure in pregnancy

In pregnancy there is a risk to both the mother and also the fetus, a syndrome now termed fetal varicella syndrome (FVS).

### Risks to the mother

- 5 times greater risk of pneumonitis

### Foetal varicella syndrome (FVS):

- Risk of FVS following maternal varicella exposure is around 1% if occurs **before 20 weeks gestation.**
- Studies have shown a very small number of cases occurring between 20-28 weeks gestation and none following 28 weeks.
- Features of FVS include skin scarring, eye defects (microphthalmia), limb hypoplasia, microcephaly and learning disabilities.

### Management of chickenpox exposure to a pregnant woman:

- If there is any doubt about the mother previously having chickenpox **maternal blood should be checked for varicella antibodies (IgM & IgG).**
- If the pregnant women is not immune to varicella she should be given **varicella zoster immunoglobulin (VZIG) as soon as possible.** RCOG and Green book guidelines suggest VZIG is effective **up to 10 days post exposure.**
- Consensus guidelines suggest **oral acyclovir** should be given if pregnant women with chickenpox **present within 24 hours of onset of the rash.**

Chickenpox exposure in pregnancy >>> first step is to check maternal varicella antibodies IgM & IgG. **Negative IgG** indicates no previous exposure to chickenpox >> **so start ttt: VZIG.**

## Ramsay Hunt syndrome

Ramsay Hunt syndrome (**herpes zoster oticus**) (**herpes zoster ophthalmicus**) is caused by the **reactivation** of the **varicella zoster virus (VZV)** in the geniculate ganglion of the **seventh** cranial nerve.

### Features:

- **Auricular pain** is often the **first** feature.
- **Facial nerve palsy.**

- **Vesicular rash around the ear** classically seen in the external auditory canal and pinna they may also be seen on the **anterior 2/3rds of the tongue and the soft palate.**
- Vesicles present on the **nasolabial folds** or on the **tip of nose** suggests involvement of the **cornea** (**Hutchinson** sign), therefore the most important consideration is **urgent ophthalmological assessment** to reduce the risk of loss of vision.
- Various ophthalmic manifestations may occur: keratitis (within first few days); periorbital and conjunctival oedema (1st week); secondary bacterial infection (staphylococci); later scarring of anterior chamber leading to glaucoma and catatract.
- Other features include **vertigo** and **tinnitus.**

### Management:

- **Oral acyclovir** and **corticosteroids** are usually given.

## Enteroviruses

- Enteroviruses are positive-sense single stranded RNA viruses.
- The family contains the Coxsackievirus, echovirus and rhinovirus as well as others.
- It is the most common cause of viral meningitis in the adult population but can cause a range of different diseases, in both adults and children.
- Although the range of diseases caused by these viruses is broad, notable disease entities include Hand, Foot and Mouth disease, herpangina and pericarditis.

## Epstein-Barr virus (EBV): associated conditions

### Malignancies associated with EBV infection:

- **Burkitt's** lymphoma (both African and sporadic Burkitt's).
- **Hodgkin's** lymphoma
- **Nasopharyngeal** carcinoma
- **HIV**-associated **CNS** lymphomas
- **Oral Hairy leukoplakia** (but it is **non**-malignant condition).

**N.B:** Adult T-cell leukaemia is associated with HTLV-1 infection.

## Burkitt's lymphoma

- It makes up about 2% of all lymphoma.
- The cells are medium-sized. There is a **very fast growing lymphoma** so presented in **a short space of time**.
- In the **African** variety, it often starts as tumours of the **jaws** or other **facial** bones.
- In the most common types seen in the **USA**, the lymphoma usually started in the **abdomen**, where it forms a large tumour mass.
- It can also spread to the brain and spinal fluid.
- 90% of patients are **men** and the average age is about **30**.
- It is a **fast growing lymphoma**, but **half** of patients are cured by **aggressive chemotherapy**.

**EX**: Male 40 y/o with 5-week history of generalized abdominal pain, nausea, weight loss, fever, night sweats, no diarrhoea, LDH 4000 >>> **Burkitt's lymphoma**. (If long history duration **>>> think of TB**).

## Oral hairy leukoplakia:

- It is **painless** shaggy **adherent white patches** affecting the **lateral borders of the tongue ±** cervical and axillary **lymphadenopathy**.
- Unlike Candida, the lesions is **adherent** and **cannot be scraped off** the tongue.
- It is caused by reactivation of EBV which occurs in patients who are **immunocompromised** like HIV.
- In most cases the diagnosis is **clinical**, but EBV can be demonstrated in epithelial cells with immunohistochemical staining.
- No specific ttt, but **HIV screening** should be done >>> **HARRT**.

# Infectious mononucleosis (IMN) (EBV) (glandular fever) (HHV-4)

- Infectious mononucleosis (glandular fever) is caused by the Epstein-Barr virus (EBV, also known as human herpesvirus 4, HHV-4) in 90% of cases.
- Less frequent causes include cytomegalovirus and HHV-6. It is most common in adolescents and young adults.
- The classic triad of sore throat, pyrexia and lymphadenopathy is seen in around 98% of patients:

### Features:

- Sore throat
- Lymphadenopathy
- Pyrexia
- Malaise, anorexia, headache
- Palatal petechiae
- Splenomegaly - occurs in around 50% of patients **and may rarely** predispose to splenic rupture
- Hepatitis
- Presence of **50% lymphocytes** with **at least 10% atypical lymphocytes.**
- **Haemolytic anaemia secondary to cold agglutins (IgM)**
- A **maculopapular, pruritic rash** develops in around 99% of patients **who take ampicillin/amoxicillin whilst they have infectious mononucleosis.**

**URTI symptoms + amoxicillin → rash, so? Glandular fever**
**Atypical lymphocytes in blood film>>>>? Glandular fever**

### Diagnosis:

- Heterophil antibody test (**Monospot test**) (**Paul-Bunnell test**).
- NICE guidelines suggest FBC and Monospot in the 2nd week of the illness to confirm a diagnosis of glandular fever.

**Management** is supportive and includes:

- Rest during the early stages, drink plenty of fluid, and avoid alcohol.
- Simple analgesia for any aches or pains.
- Consensus guidance in the UK is to **avoid playing contact sports for 4 weeks** after having glandular fever **to reduce the risk of splenic rupture.**

## Measles

### Overview:

- **RNA** paramyxovirus
- Spread by droplets
- Infective from prodrome until 4 days after rash starts
- Incubation period = 10-14 days

## Features:

- prodromal phase
  - irritable
  - conjunctivitis
  - fever
- Koplik spots
  - typically develop before the rash
  - white spots ('grain of salt') on the buccal mucosa
- rash
  - starts behind ears then to the whole body
  - discrete maculopapular rash becoming blotchy & confluent
  - desquamation that typically spares the palms and soles may occur after a week
- diarrhoea occurs in around 10% of patients

## Investigations

- IgM antibodies can be detected within a few days of rash onset

## Complications:

- **Encephalitis**: typically occurs 1-2 weeks following the onset of the illness)
- **Subacute sclerosing pan-encephalitis**: very rare, may present 5-10 years following the illness
- Giant cell **pneumonia**
- Febrile convulsions
- Keratoconjunctivitis, corneal ulceration
- Diarrhoea
- ↑ incidence of appendicitis
- Myocarditis

**N.B:** Pancreatitis and infertility may follow mumps infection not measles.

## Management of contacts:

- If a child not immunized against measles comes into contact with measles then **MMR** should be offered (vaccine-induced measles antibody develops more rapidly than that following natural infection).
- This should be given **within 72 hours.**

## AMS (Atypical Measles Syndrome)

It occurs in persons who were **incompletely immunised against measles**.

This may occur either because they were given the old killed virus measles vaccine (no longer available) or they were given the attenuated (weakened) live measles vaccine which had been inactivated due to improper storage.

The latter **does not prevent measles** but causes an alteration in its expression, resulting in AMS.

**Pneumonia** is a common complication and may persists for months.

**Virus isolation, serological** studies, or both may necessary to confirm the diagnosis.

Rocky Mountain Spotted Fever (RMSF) is a viable differential diagnosis.

is >>> **Hydrops fetalis**.

## Reye's syndrome

Reye's syndrome is a **severe, progressive encephalopathy** affecting children that is accompanied by **fatty infiltration** of the **liver, kidneys** and **pancreas**.

**The aetiology of Reye's syndrome** is not fully understood although there is a known association with **aspirin** use and a **viral** cause has been postulated.

The peak incidence is **2 years of age**, features include:

- May be history of **preceding viral** illness and/or **aspirin** use.
- **Encephalopathy**: confusion, **seizures**, cerebral oedema, coma.
- **Fatty infiltration** of the liver, kidneys and pancreas.
- **Hypoglycaemia.**

**Management is supportive:**

Although the prognosis has improved over recent years there is still a mortality rate of 15-25%.

# Parvovirus B19 (fifth 5th disease) or (slapped cheek syndrome)

It is a **DNA** virus which causes a variety of clinical presentations.

It was identified in the **1980's** as the cause of **erythema infectiosum**.

Erythema infectiosum (also known as fifth disease or "slapped cheek syndrome").

## Features:

- Systemic constitutional symptoms: fever, headache, lethargy.
- Slapped cheek rash spreading to proximal arms and extensor surfaces.
- The rash may spread to the rest of the body but unlike many other rashes, it only rarely involves the palms and soles.
- However, in others there is a noticeable rash which appears after a few days. The rose-red rash makes the cheeks appear bright red, hence the name 'slapped cheek syndrome'.
- May be asymptomatic.
- **Pancytopenia** in **immunosuppressed** patients.
- **Parvovirus B19-related red cell aplasia** is associated with **HIV >>> anaemia without reticulocytosis** and **BM aspirate** will show **pure red cell aplasia.**
- Infection can be confirmed by IgM serology or PCR.
- **Aplastic crises**: e.g. **in sickle cell disease** (Parvovirus B19 suppresses erythropoiesis for about a week so aplastic anemia is rare unless there is a chronic hemolytic anaemia).
- It is known to cause **fetal anaemia, hydrops fetalis** (2nd trimester) and **IUFD.**
- Parvovirus B19 infection may account for up to 20% of non-immune cases of **hydrops fetalis**.
- Autopsy studies indicates that highest viral concentration are found in bone marrow and myocardium.

The most common complication associated with fetal slapped cheek infection

# Rabies

- Rabies is a viral disease that causes an acute progressive encephalitis.
- The rabies virus is classed as a RNA rhabdovirus and has a bullet shaped capsid.
- Incubation period is 1 – 3 months.
- It is commonly transmitted by bat, raccoon and skunk bites. Following a bite the virus travels up the nerve axons towards the CNS in a retrograde fashion.
- **Once symptoms begin, treatment is largely useless.**
- Patients usually die within days to weeks after presentation.

## Features:

- **Prodrome**: headache, fever, agitation.
- **Hydrophobia**: water-provoking muscle spasms.
- **Hypersalivation.**
- **Negri bodies**: cytoplasmic inclusion bodies found in infected neurons.

There is now considered to be **'no risk'** of developing rabies following an animal bite in the UK and the majority of developed countries.

**If the suspicion of rabies is low**, i.e. the dog seemed healthy, only minor abrasions through double layers cloths, abrasions were washed well; so prophylaxis is not indicated.

Instead, **the animal (dog) should be confined and observed daily for 10 days** by a vet and **if it exhibits signs of rabies** during the 10-day observation period, the patient should immediately receive **prophylaxis** and the animal should be **killed** and its **brain tissue tested for rabies**.

**If the bite occurred in an area where rabies is endemic,** immediate post exposure prophylaxis is warranted, either with locally produced biologic agents or those obtained from the closest major urban area or country.

Following an animal bite in at risk countries:

- If an individual is already immunised then 2 further doses of vaccine should be given.
- If not previously immunised then human rabies immunoglobulin (HRIG) should be given along with a full course of vaccination.

Rabies - following possible exposure >>>
Give **human rabies immunoglobulin (HRIG) + full course of vaccination.**

## Zika virus conditions

Zika is a mosquito-borne infection caused by Zika virus, a member of the genus flavivirus and family Flaviviridae.
It was first isolated from a monkey in the Zika forest in Uganda in 1947.

Transmission is usually via the bite of an infected Aedes mosquito, although a small number of cases of sexual transmission have been reported.
There is increasing evidence of transmission via the placenta from mother to fetus.

The majority of people infected with Zika virus have no symptoms. For those with symptoms, Zika virus tends to cause a mild, short-lived (2 to 7 days) febrile disease.

**Signs and symptoms suggestive of Zika virus infection may include a combination of the following:**

- fever
- rash
- arthralgia/arthritis
- conjunctivitis
- myalgia
- headache
- retro-orbital pain
- pruritus

Serious complications in adults are not common, although the virus has been associated with Guillain-Barre syndrome.
Scientific consensus however has linked Zika with microcephaly and other congenital abnormalities, which has led the World Health Organisation (WHO) to declare a Public Health Emergency of International Concern (PHEIC).

## Orf

Orf is generally a condition found in **sheep and goats** although it can be transmitted to humans. It is caused by the **parapox virus**.

**In animals:** 'Scabby' lesions around the mouth and nose.
**In humans:**

- Generally affects the **hands and arms** of the **farmer**.
- **Initially small, raised, red-blue papules.**
- **Later** may **increase in size to 2-3 cm** and become flat-topped and **haemorrhagic.**

# Retroviruses

## HIV: the virus

### Basics:

- HIV is a **RNA** retrovirus of the lentivirus genus (lentiviruses are characterized by a **long incubation period**).
- Two variants - HIV-1 and HIV-2.
- HIV-2 is more common in West Africa, has a lower transmission rate and is thought to be less pathogenic with a slower progression to AIDS.

### Basics structure:

- Spherical in shape with two copies of single-stranded RNA enclosed by a capsid of the viral protein p24.
- A matrix composed of viral protein p17 surrounds the capsid.
- Envelope proteins: gp120 and gp41.
- Pol gene encodes for viral enzymes reverse transcriptase, integrase and HIV protease.

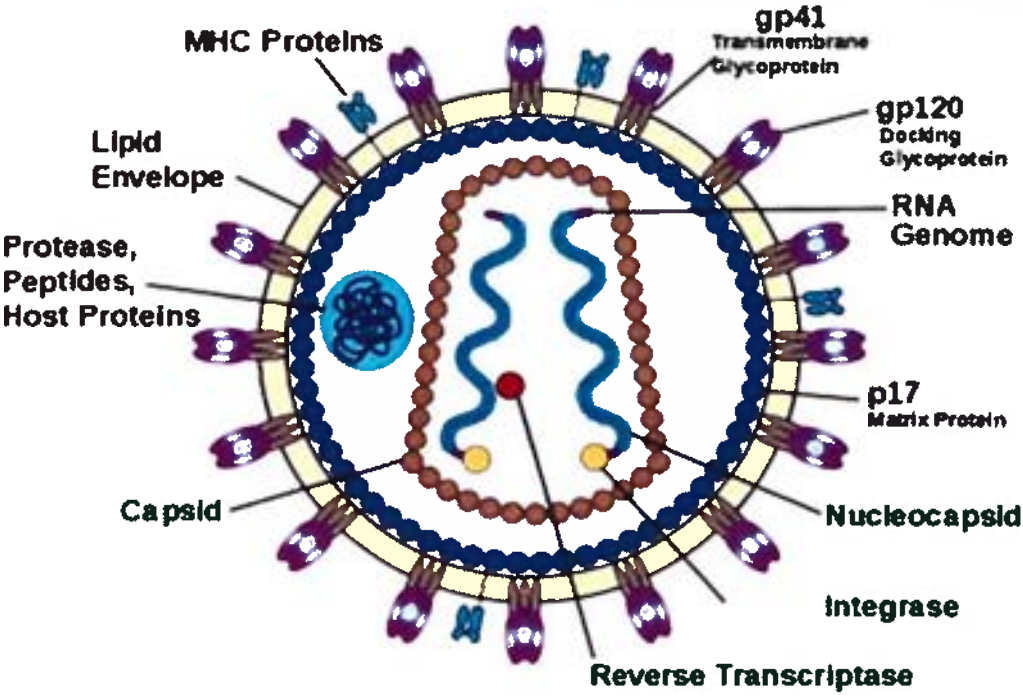
### Cell entry:

- HIV can infect **CD4** T cells, **macrophages** and **dendritic** cells.
- Gp120 binds to CD4 and CXCR4 on T cells and CD4 and CCR5 on macrophages.
- Mutations in CCR5 can give immunity to HIV.

### Replication:

- **After entering** a cell the enzyme **reverse transcriptase creates dsDNA from the RNA** for **integration into the host cell's genome.**

Regarding targets for anti-HIV drugs. The role of **reverse transcriptase** in HIV infection >>>**Transcribes viral RNA to host DNA.**




## HIV: Seroconversion (Acute HIV infection)

HIV seroconversion illness is symptomatic in 60-80% of patients and typically presents as a **glandular fever type** illness.

Increased symptomatic severity is associated with poorer long term prognosis.

**It typically occurs 3-12 weeks after infection**

Typical symptoms include (**4**): **fever**, **pharyngitis**, **lymphadenopathy** and a widespread **maculopapular rash**.
The illness closely resembles infectious mononucleosis.
NB: Acute Epstein-Barr virus (**EBV**) is **less** common in adults as it is usually acquired in **teenage** years and a diffuse macular rash most often occurs **following** administration of ampicillin.

### Features:

- sore throat
- lymphadenopathy
- malaise, myalgia, arthralgia
- diarrhoea
- maculopapular rash
- mouth ulcers
- rarely meningoencephalitis

## Diagnosis:

- HIV Ab may not be present, so a negative HIV Ab doesn't exclude it.
- **HIV (RNA) PCR** and **P 24 antigen** tests can confirm diagnosis.

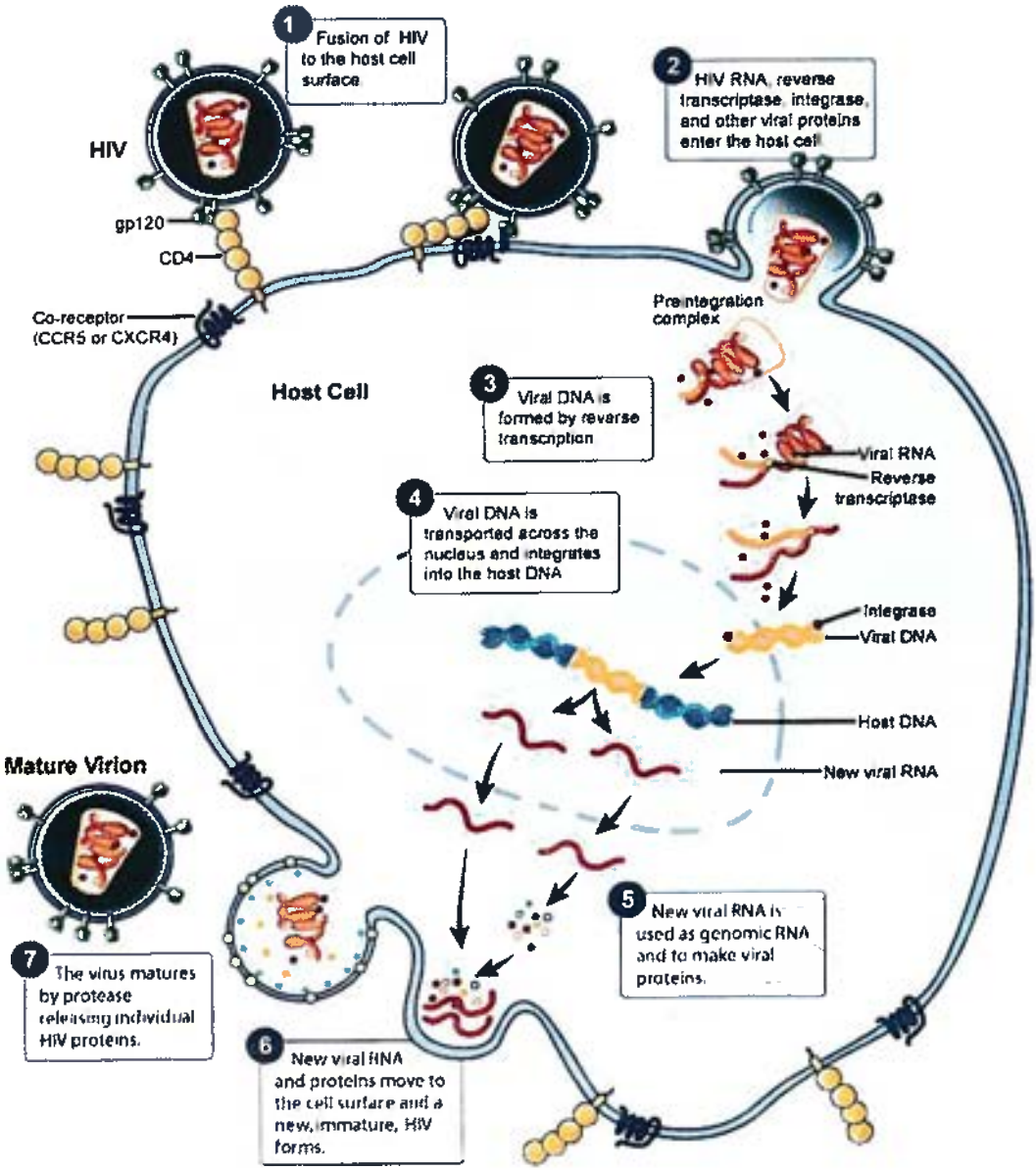
**EX**: **Man** returns from **business** trip abroad with **maculopapular rash** and **flu-like illness** (fever, sore throat), generalised **lymphadenopathy** >>> think **HIV seroconversion.**
**EX:** For questions involving **businessmen** always consider sexually transmitted infections.
**N.B**: The HIV prevalence rate in **Kenya** and **Uganda** is currently around 8%.

# HIV Immunology

The following immunological changes are seen in **progressive HIV**:

- ↓ CD4 count (N > 500/MicroL)
- ↓ NK cell function
- ↓ delayed type IV hypersensitivity responses
- Increased B2-Microglobulin (IBM) }
- Decreased IL-2 production (DIL=DELL) } **IBM & DELL**
- Polyclonal B-cell activation

Normal CD4 = 300-1300 x 106/L


1 Fusion of HIV to the host cell surface
HIV
gp120
CD4
Co-receptor (CCR5 or CXCR4)
2 HIV RNA, reverse transcriptase, integrase, and other viral proteins enter the host cell
Pre-integration complex
Host Cell
3 Viral DNA is formed by reverse transcription
Viral RNA
Reverse transcriptase
4 Viral DNA is transported across the nucleus and integrates into the host DNA
Integrase
Viral DNA
Host DNA
New viral RNA
Mature Virion
5 New viral RNA is used as genomic RNA and to make viral proteins.
7 The virus matures by protease releasing individual HIV proteins.
6 New viral RNA and proteins move to the cell surface and a new, immature, HIV forms.

An illustration model of the HIV Replication Cycle. Each step of the cycle is numbered and concisely described. Credit: NIAID

# HIV: immunisation

The Department of Health 'Green book' on immunisation defers to the British HIV Association for guidelines relating to immunisation of HIV-infected adults.

| Vaccines that can be used in all HIV-infected adults | Vaccines that can be used if CD4 > 200 | Contraindicated in HIV-infected adults |
|---|---|---|
| - Hepatitis A<br>- Hepatitis B<br>- Haemophilus influenzae B (Hib)<br>- Influenza-parenteral<br>- Japanese encephalitis<br>- Meningococcus-MenC<br>- Meningococcus-ACWY I<br>- Pneumococcus-PPV23<br>- Poliomyelitis-parenteral (IPV)<br>- Rabies<br>- Tetanus-Diphtheria (Td) | -MMR.<br>-Varicella.<br>-Yellow Fever. | - **Cholera** CVD103-HgR.<br>- **Influenza-intranasal.**<br>- **Oral polio (OPV).**<br>**-Tuberculosis (BCG).** |

# HIV: Highly Active Anti-Retroviral Therapy (HAART)

(HAART) involves a combination of at **least three drugs**, typically two nucleoside reverse transcriptase inhibitors **(NRTI)** and either a protease inhibitor **(PI)** or a non-nucleoside reverse transcriptase inhibitor **(NNRTI).**

This combination both decreases viral replication and also reduces the risk of viral resistance emerging.

**Start** HAART in HIV when **CD4 < 350 * $10^6$/l**

**Nucleoside analogue reverse transcriptase inhibitors (NRTI):**

- Ex: **Zidovudine (AZT),** didanosine, lamivudine, stavudine, zalcitabine, abacavir.
- General NRTI side-effects:
  - **NRTI-related cardiomyopathy**: due to mitochondrial toxicity (ttt: replace Zidovudine with another one).
  - Peripheral neuropathy
- **Zidovudine (AZT) SE: Macrocytosis (Macrocytic anaemia: due to RBCs hypoplasia or aplasia), BM depression,** Pt can become transfusion-dependent in severe cases, **myopathy up to rhabdomyolysis, black_nails, fat redistribution** (peripheral fat loss and ↑ abdominal obesity) and **insulin resistance.**
- Didanosine: **pancreatitis.**

**Non-nucleoside reverse transcriptase inhibitors (NNRTI):**

- Examples: **Nevirapine, Efavirenz.**
- Side-effects: P450 enzyme interaction (Nevirapine induces), rashes.
- Nevirapine can cause **acute hepatitis** and **skin rash** as a part of **hypersensitive reaction**

**Protease inhibitors (PI):**

- Examples: **Indinavir**, Nelfinavir, Ritonavir, Saquinavir, **Lopinavir.**
- Inhibits a protease needed to make virus able to survive outside the cell.
- Side-effects: **diabetes**, **hyperlipidaemia** (especially ↑**TG**), central obesity, buffalo hump, P450 enzyme inhibition.
- **Indinavir**: SE:
  - Asymptomatic hyperbilirubinaemia,
  - **Crystal nephropathy** & **renal stones**: there is drug-drug interactions leading to ↑ indinavir concentration like co-trimoxazole so induce more Crystal nephropathy, ttt: good hydration Normal saline 2-3 L/day.
- **Tenofovir** is associated with **acute renal impairment**
- **Ritonavir**: a potent inhibitor of the P450 system.
- **Atazanavir** causes isolated **hyperbilirubinaemia** without elevate aminotransferases (Gilbert like picture).

| HIV: **HAART - P450 interaction**: |
|---|
| • Nevirapine (a NNRTI): **induces** P450. |
| • Protease inhibitors (PI): **inhibits** P450. |
| **HIV drugs, rule of thumb:** |
| • NRTIs end in 'ine' |
| • NNRTIs: Nevirapine, Efavirenz |
| • Pis: end in 'vir' |

## Immune reconstitution syndrome (IRS):

Some patients after receiving **HAART** will develop an exacerbation of symptoms (more weight loss, drenching night sweats and malaise), signs or radiological manifestation of **TB**.

This has been well described in patients without HIV infection who have a period of depressed immunity, but appears to occur more commonly in HIV-positives patients.

The aetiology is unknown but may be due to **HAART-related reconstitution of immunity** leading to abnormal immune response to tubercle antigens released by dead or dying bacilli.

IRS can also occur with other with other infections such as CMV and toxoplasmosis.

**EX**: Pt with HIV started HAART then 3 weeks later he presents extremely unwell with 5 kg weight loss, drenching night sweats and malaise >>> **Immune reconstitution syndrome (IRS).**

## HIV: Pneumocystis jiroveci pneumonia (=PCP)

Whilst the organism Pneumocystis carinii is now referred to as Pneumocystis jiroveci, the term Pneumocystis carinii pneumonia (PCP) is still in common use.

- Pneumocystis jiroveci is a **unicellular eukaryote**, generally classified as a **fungus** but some authorities consider it a **protozoa**.
- PCP is the most common opportunistic infection in AIDS.
- **All** patients with a **CD4 count < 200/mm³** >>> should receive **PCP prophylaxis**.

### Features:

- Dyspnoea
- Dry cough
- Fever
- Very few chest signs
- **Pneumothorax** is a common complication of PCP.
- Extra pulmonary manifestations are rare (1-2% of cases), may cause:
  - HSM
  - Lymphadenopathy
  - Choroid lesions

### Investigation:

- CXR: typically shows bilateral interstitial pulmonary infiltrates but can present with other x-ray findings e.g. lobar consolidation. **May be normal**.
- **Exercise-induced desaturation.**
- Sputum often fails to show PCP.
- **Bronchoalveolar lavage (BAL)** often needed to demonstrate PCP (**silver stain shows characteristic cysts**).

### Management:

- **Co-trimoxazole IV.**
- **Clindamycin:** can be used in ttt not for prophylaxis.
- **IV pentamidine** in severe cases.
- **± Steroids (high dose Methylprednisolone IV) if hypoxic if PO2 < 9.3 kPa (< 70 mmHg)** as this is an indicator of **severe disease**, then steroids reduce risk of respiratory failure by 50% and death by a third.

Patients often deteriorate after starting therapy for PCP as the pneumonitis worsens due to the inflammation associated with dying pneumocysts.
In patients with a PO2 < 70 mmHg, oral prednisolone is added to reduce the inflammatory effect.
So, treatment is **Co-trimoxazole IV + Prednisolone IV**.

**NB**: Immune Reconstitution Uveitis: Occurs in AIDS in response to immune system recovery, there is granulomatous uveitis that leads to reduced vision and eye discoloration.

**For prevention of PCP:**

- **Co-trimoxazole orally, it can't be given as a nebulizer form.**
- **Pentamidine nebulizer.**
- **Dapsone**, but can cause haemolysis esp. in G6PD deficiency.

**NB**: With an abnormal CD4 count patients with HIV are at risk for invasive streptococcal infection secondary to streptococcal pneumonia. All patients with HIV should have **routine pneumococcal vaccination**.
**NB**: In patients with well-controlled HIV and a **normal CD4 count pneumonia** can be managed as an outpatient using **CURB scoring** and antimicrobial prescribing guidelines, but with an awareness of the possibility of **drug interactions (like Clarithromycin** is a **CYP3A4 inhibitor)**.

## HIV: biliary & pancreatic disease (HIV Cholangiopathy)

- The most common cause of biliary disease in patients with HIV is **sclerosing cholangitis** due to infections such as Cryptosporidium, CMV and Microsporidia.
- **MRCP**/ERCP for diagnosis.
- **Pancreatitis** in the context of HIV infection may be 2ry to anti-retroviral treatment (especially **didanosine**) or by opportunistic infections e.g. CMV.

## HIV: diarrhoea

Diarrhoea is common in patients with HIV.
This may be due to the effects of the virus itself (HIV enteritis) or opportunistic infections.

**Possible causes:**

- **Cryptosporidium** + other protozoa (most common)
- Mycobacterium avium intracellulare
- CMV
- Giardia

### Cryptosporidium:

- It is the most common infective cause of diarrhoea in HIV patients.
- It is an intracellular protozoa and has an incubation period of 7 days.
- Presentation is very variable, ranging from mild to severe diarrhoea.
- **A modified Ziehl-Neelsen stain (acid-fast stain) of the stool** may reveal the **characteristic red rounded oocysts of Cryptosporidium against a blue-green background**. (NOT Cryptosporidium PCR of stool >> it's used only as a research tool).
- Treatment is difficult, with the mainstay of management being **supportive** therapy (**Nitazoxanide** is licensed in the US for immunocompetent patients).

### Mycobacterium avium intracellulare (MAI):

- It is an atypical mycobacteria seen with the **CD4 count is below 50**.
- Typical features include fever, sweats, abdominal pain and diarrhoea.
- MAI can present with both **abdominal** and **pulmonary** pathology (pulmonary infiltrate, hilar LN) and with **anaemia**.
- There may be hepatomegaly and deranged LFTs.
- Diagnosis is made by blood cultures and bone marrow examination.
- Management is with Rifampicin, Ethambutol and clarithromycin.
- Patients with a CD4 count below 50 cells/mm3 should receive MAI inhibitor.

## HIV and pregnancy

With the increased incidence of HIV infection amongst the heterosexual population there are an increasing number of HIV positive women giving birth in the UK.
In London the incidence may be as high as **0.4% of pregnant women**.
The aim of treating HIV positive women during pregnancy is to minimise harm to both the mother and fetus, and to reduce the chance of vertical transmission.

### Factors which reduce vertical transmission (from 25-30% to 2%):

- Maternal antiretroviral therapy.
- Mode of delivery (caesarean section).
- Neonatal antiretroviral therapy.
- Infant feeding (bottle feeding).

NICE guidelines recommend offering **HIV screening** to **all pregnant** women.

**1) Antiretroviral therapy:**

- All pregnant women should be offered antiretroviral therapy regardless of whether they were taking it previously.
- If women are not currently taking antiretroviral therapy the RCOG recommend that it is commenced **between 28 and 32 weeks of gestation** and should be continued intrapartum.
- **BHIVA** recommend that antiretroviral therapy may be started at an **earlier** gestation depending upon the individual situation.

**2) Mode of delivery:**

- **Vaginal** delivery is recommenced if viral load is less than 50 copies/ml at 36 weeks, otherwise **caesarean section** is recommended.
- A **Zidovudine IV infusion** should be started 4 hours before beginning the caesarean section.

**3) Neonatal antiretroviral therapy:**

- **Zidovudine** is usually administered orally to the neonate if maternal viral load is <50 copies/ml. Otherwise **triple ART** should be used.
- Therapy should be continued **for 4-6 weeks**.

**4) Infant feeding:**

- In the UK all women should be advised **not** to breast feed.

## HIV: Kaposi's sarcoma (KS)

- Caused by **HHV-8** (human herpes virus 8).
- Presents as **purple papules or plaques** on the **skin or mucosa** (e.g. **gastrointestinal** and **respiratory** tract).
- Skin lesions may later ulcerate.
- Respiratory involvement may cause massive **haemoptysis** and pleural effusion.
- Pulmonary Kaposi's sarcoma is found in 6-30% of patients with HIV, and is the most common tumour seen.
- In patients with **cutaneous** Kaposi's, **up to 75% have pulmonary Kaposi's** tumours on endobronchial biopsy.
- Radiotherapy + resection.

### Treatment

- Retinoid gel may be of value.

Kaposi's sarcoma in a patient with HIV

## HIV: Skin rash (see pic)

**Eosinophilic folliculitis** is the **most common** of the popular pruritic disorders in HIV infection.

The underlying pathophysiology is unknown.

It tends to occur when the **CD count is below 300 cell/mm3**.

It presents as many excoriated papules and pustules on the chest, back and extensor surface of the arm.

Swabs are usually negative on culture.

On biopsy, a mixed infiltrate of mainly eosinophils with some neutrophils.

It tends to be resistant to most ttt although **HAART** does improve it.

## HIV and Eye

**CMV retinitis** is the most common cause of eye disease and **blindness** in HIV patients.

CMV retinitis is a slowly progressive disorder; visual loss may occur **suddenly** as a result of haemorrhage or retinal detachment, or **more slowly** due to progressive involvement of the macula and optic nerve.

## Treatment:

- **Foscarnet IV:** trial evidence suggests that viral clearance occurs marginally more quickly in patients treated with Foscarnet and less resistance is seen versus Gancyclovir.
- **Gancyclovir IV 10 mg/kg/day for at least 3 weeks** or until retinitis is quiescent, follow up of CBC is recommended to be monitored during Gancyclovir therapy as it is myelosupressive.
- **Cidofovir IV:** it can be used if both Foscarnet and Gancyclovir are contraindicated or there is a failure to response to one of them.

**NB:** HIV patient with loss of vision >>> CMV retinitis >>> **Treatment:** Foscarnet IV

# HIV: Neuro-complications

| Generalised | Focal |
|---|---|
| 1) Encephalitis: | 1) Toxoplasmosis: |
| 2) Cryptococcus: | 2) Lymphoma: |
| 3) PML | 3) Tuberculosis: |
| 4) AIDS dementia complex: | |

## Generalised neurological disease:

### 1) Encephalitis:

- May be due to CMV or HIV itself
- HSV encephalitis but is relatively rare in the context of HIV
- CT: oedematous brain

### 2) Cryptococcus:

- **Most common fungal infection of CNS.**
- Headache, fever, malaise, nausea/vomiting, seizures, focal neurological deficit.
- Cryptococcus enters the blood through the lungs so that up to third of patients will report a **pneumonitis** in the weeks preceding systemic cryptococcal infection.
- CSF: **high opening pressure, ↑ lymphocytes, India ink test positive.**
- CT: **Meningeal enhancement, cerebral oedema.**
- Meningitis is typical presentation but may occasionally cause a space occupying lesion.
- Treatment: **Amphotericin B IV (1.5 mg/kg per day) + Flucytosine (5FC) IV (100 mg/kg/d in 4 divided doses) for 2 weeks ± Fluconazole** (400 mg/day for 8 weeks).

**EX**: Any pt with HIV and has meningitis like picture >>>? Cryptococcus meningo-encephalitis >>> Amphotericin B IV + Flucytosine IV.

### 3) Progressive multifocal leukoencephalopathy (PML):

- Widespread **demyelination** lesions.
- Due to infection of oligodendrocytes by **JC papova virus** (**polyoma** DNA **virus**).
- It occurs almost **exclusively** in **immunosuppressed** individuals such as patients with AIDS, leukaemia or tumours, or those undergoing organ transplantation.
- Before the advent of HIV therapy, up to 4% of patients with AIDS had PML.
- The lesions may occur anywhere but are usually in the cerebral hemispheres, less often in the cerebellum and brainstem and rarely in the spinal cord.
- Almost **any neurological sign** can be part of the clinical spectrum either motor, sensory or cerebellar signs depending on the white matter areas being affected.
- Symptoms, **subacute** (**insidious**) onset: **visual, motor (hemiparesis), cognitive (Dementia), speech, mental** and **behavioural** changes. **Headache** and **neck stiffness** are less common. It progresses faster than the AIDS-dementia complex.
- The PML **progresses rapidly** and the patient is **severely disabled**, eventually becoming **demented, blind** and **paralyzed** and finally there is coma and death.
- CT: single or multiple lesions, **no mass effect**, don't usually enhance and also it may be normal.
- **MRI** is better - high-signal **demyelinating multiple white matter** lesions are seen.
- CSF is usually normal, but protein may be elevated slightly.
- Brain biopsy has a sensitivity of 74-92% and a specificity of 92-100%.
- **JC virus can usually be isolated** on **PCR** **of** **CSF** in PML and also **JC virus antibodies** may be demonstrated.
- **No specific ttt**, however commencing **HAART can** improve symptoms in some patients although some can deteriorate.

### 4) AIDS dementia complex (HIV encephalopathy):

- Caused by HIV virus itself
- Symptoms: behavioural changes, cognitive dysfunction, motor impairment.
- Typically the presentation is of diffuse subcortical dementia, **poor balance, poor co-ordination, ataxic gait, generalised motor**

**weakness diffuse hyperreflexia** and patient become **incontinent** and develop seizure.

- CT: cortical and subcortical **atrophy** with wide sulci

## Focal neurological lesions:

### 1) Toxoplasmosis:

- Accounts for around **50%** of cerebral lesions in patients with HIV.
- Constitutional symptoms, headache, confusion, drowsiness.
- Cerebral toxoplasmosis is usually cause UMNL rather than lower.
- CT: usually **single or multiple ring enhancing lesions, mass** effect may be seen.
- Management: **Sulfadiazine + Pyrimethamine + Folinic acid.**

**EX**: Pt with **HIV** and **TB** already on HAART and 4 drug anti-TB, then he develop a grand mal seizure with CT brain revealed a **solitary focal lesion** in the LT internal capsule >>> D.D: **cerebral toxoplasma**, lymphoma and a tuberculoma, and so **immediate commence with Sulfadiazine + Pyrimethamine**
MRI and toxoplasma serology would be very useful but they are not as urgent as starting toxoplasma ttt.
**LP is relatively contraindicated if there is ↑ ICP.**

### 2) Primary CNS lymphoma:

- Accounts for around **30%** of cerebral lesions
- Associated with the **EBV** (Epstein-Barr virus)
- CT: **single or multiple ring enhancing lesions**

Differentiating between toxoplasmosis and lymphoma is a common clinical scenario in HIV patients.
It is clearly important given the vastly different treatment strategies.

| Toxoplasmosis | Lymphoma |
|---|---|
| • **Multiple** lesions<br>• Ring or nodular enhancement<br>• Thallium SPECT **negative** | • **S**ingle lesion.<br>• **S**olid enhancement.<br>• Thallium SPECT **p**ositive. |

**NB**: Given the more limited availability of SPECT compared to CT many patients are treated empirically on the basis of scoring systems, for example there is a 90% likelihood of toxoplasmosis if all of the following criteria are met:

- Toxoplasmosis IgG in the serum
- CD4 < 100 and not receiving prophylaxis for toxoplasmosis
- Multiple ring enhancing lesions on CT or MRI

### 3) Tuberculosis:

- Much less common than toxoplasmosis or primary CNS lymphoma
- CT: single enhancing lesion

## HIV associated nephropathy (HIVAN)

**It is characterised by:**

- **Low CD4 count**
- **Nephrotic range proteinuria.**
- **Normal BP.**
- Normal or increased kidney size on US.
- FSGS by renal biopsy.

**Treatment:** Initiate **antiretroviral** therapy + ACEI (if not contraindicated).

## HIV and Addison's disease

Addison's disease can occur in patients with HIV secondary to **CMV-adrenalitis** which is an **immune reconstitution syndrome.**

The two causes of Addison's in immunocompromised patient like **HIV: are (CMV-Adrenalitis)** and **TB**.

# Sexual Transmitted Infections (STIs)

## Chlamydia

Chlamydia is **the most prevalent sexually transmitted infection in the UK** and is caused by Chlamydia trachomatis, an obligate intracellular pathogen.

Approximately **1 in 10 young women** in the UK have Chlamydia.

The incubation period is around 7-21 days, although it should be remembered a large percentage of cases are **asymptomatic** so unfortunately usually the diagnosis is missed.

Non-specific urethritis (**NSU**) is caused by **Chlamydia** in **60%** of cases.

**Azithromycin** and **Doxycycline** are both commonly used in ttt of **NSU**. NSU can be **non-infective** in origin e.g. after a night of heavy alcohol consumption, in men who use antiseptic to clean their urethra or post vigorous sex or masturbation.

The possibility of **pelvic infection** in **young** women of **reproductive** age who complain of **back ache** with no restriction of spinal movement, particularly **chlamydia**, should always be borne in mind especially when with normal urine analysis and elevated CRP.

### Features:

- **Asymptomatic** in around 80% of women and 50% of men.
- Women: cervicitis (discharge, bleeding), dysuria.
- Men: **urethral discharge, dysuria & acute epididymitis (D.D. Torsion testis).**

### Potential complications:

- Epididymitis.
- PID (like Endometritis).
- ↑ Incidence of ectopic pregnancies.
- Infertility.
- Reactive arthritis.
- Periappendicitis
- Perihepatitis (**Fitz-Hugh-Curtis syndrome**).

### Investigation:

- Traditional cell culture is no longer widely used

- **Chlamydial Nuclear acid amplification tests (NAATs)** are now rapidly emerging as the investigation of choice with high sensitivity 95%.
- **Urine** (first void urine sample), **vulvovaginal swab** or **cervical swab** may be tested using the **NAAT** technique.

## Screening:

- In England the National *Chlamydia* Screening Programme (NCSP) is open to all men and women aged 15-24 years.
- The 2009 SIGN guidelines support this approach, suggesting screening all sexually active patients aged 15-24 years.
- Relies heavily on opportunistic testing.

## Management:

- **doxycycline (7 day course) if first-line**
  - this is now preferred to azithromycin due to concerns about *Mycoplasma genitalium*. This infection is often coexistant in patients with *Chlamydia* and there is evidence of rising levels of macrolide resistance, hence why doxycycline is preferred
  - if doxycycline is contraindicated / not tolerated then either azithromycin (1g od for one day, then 500mg od for two days) should be used
- if pregnant then **azithromycin, erythromycin or amoxicillin** may be used. The SIGN guidelines suggest azithromycin 1g stat is the drug of choice 'following discussion of the balance of benefits and risks with the patient'
- Patient should refrain from intercourse for a period of 7 days.
- Contact partner notification should be encouraged.
- Patients diagnosed with Chlamydia should be offered a choice of provider for initial partner notification - either trained practice nurses with support from GUM, or referral to GUM.
- For men with symptomatic infection all partners **from 4 weeks prior to** the onset of symptoms should be contacted.
- For women and asymptomatic men all partners **from the last 6 months** or the most recent sexual partner should be contacted.
- **Contacts of confirmed Chlamydia cases should be offered treatment prior to the results of their investigations being known (treat then test).**
- **A test of cure** should be carried out following treatment.

**EX**: A 20-year-old man presents with dysuria and a urethral discharge. Gram staining of the urethral discharge demonstrates **neutrophils** but **no bacteria**. The most likely causative organism >>> **Chlamydia trachomatis**

**Chlamydia psittaci (psittacosis) = parrot disease (parrot fever):**
It is characterized by malaise, fever, myalgia and pneumonia.
Exposure to an ill bird and a rash (Horder's spots) are pathognomonic.
treatment: Erythromycin or tetracycline is the drug of choice.

**exam: A swab taken in the clinic showed a Gram-negative diplococcus and treatment with IM ceftriaxone was given. his symptoms have not resolved. What is the most likely explanation?**
**>> Co-existent *Chlamydia* infection** (Co-existent infection with *Chlamydia* is extremely common in patients with gonorrhoea).

## Gonorrhoea

Gonorrhoea is caused by the **Gram-negative diplococcus** Neisseria gonorrhoea. Acute infection can occur **on any mucous membrane surface,** typically genitourinary but also rectum and pharynx.
The incubation period of gonorrhoea is 2-5 days.

### Features:

- Males: urethral discharge, dysuria.
- Females: cervicitis e.g. leading to vaginal discharge.
- Rectal and pharyngeal infection is usually asymptomatic.

Local complications that may develop include urethral strictures, epididymitis and salpingitis (hence may lead to **infertility**). Disseminated infection may occur.

### Management:

- ciprofloxacin used to be the treatment of choice. However, there is increased resistance to ciprofloxacin (around 36% in the UK) and therefore cephalosporins are now more widely used
- there was a change in the 2019 British Society for Sexual Health and HIV (BASHH) guidelines. Previously the first-line treatment was IM ceftriaxone + oral azithromycin.
- **The new first-line treatment is a single dose of IM ceftriaxone 1g** (i.e. no longer add azithromycin). If sensitivities are known (and the organism is sensitive to ciprofloxacin) then a single dose of oral ciprofloxacin 500mg should be given
- if ceftriaxone is refused (e.g. needle-phobic) **then oral cefixime 400mg** (single dose) **+ oral azithromycin 2g** (single dose) should be used

Cephalosporins are now the treatment of choice for Gonorrhoea

**Disseminated gonococcal infection (DGI)** and gonococcal arthritis may also occur, with gonococcal infection being the most common cause of septic arthritis in young adults.

The pathophysiology of DGI is not fully understood but is thought to be due to haematogenous spread from mucosal infection (e.g. asymptomatic genital infection).

Initially there may be a classic **triad** of symptoms: **tenosynovitis**, **migratory polyarthritis and dermatitis.**

Later complications include septic arthritis, endocarditis and Perihepatitis (Fitz-Hugh-Curtis syndrome).

**Key features of disseminated gonococcal infection (DGI):**
1) Tenosynovitis
2) Migratory polyarthritis
3) Dermatitis (lesions can be maculopapular or vesicular)

**Co-existent infection with Chlamydia** is extremely common in patient with gonorrhoea.

**EX:** Pt with gonorrhoea and received ceftriaxone 250 mg IM single dose, but unfortunately his symptoms have not resolved.
What is the most likely explanation? >> Co-existent infection with Chlamydia.

**Infertility** secondary to pelvic inflammatory disease (**PID**) is the most common complication of **gonorrhoea**. It is the second most common cause of PID after Chlamydia.
**Rectal gonococcal infection** due to unprotected **male anal homosexual** sex >>> Investigation of choice is **rectal NAAT swab** (Nucleic Acid Amplification Testing), before treatment he should be screened for other **STDs** including HIV and the **other** male partner should also be screened.

**exam: H/O a purulent urethral discharge. A sample of the discharge is shown to be a Gram-negative diplococcus. What is the most appropriate antimicrobial therapy?**
**>> Intramuscular ceftriaxone stat dose + oral azithromycin stat dose**

**exam: What is the most likely complication from repeated *Neisseria gonorrhoea* infection?**
**>> Infertility:** (Infertility secondary to pelvic inflammatory disease (PID) is the most common complication of gonorrhoea)

## Non-gonococcal urethritis (NGU)

Non-gonococcal urethritis (NGU, sometimes referred to as non-specific urethritis) is a term used to describe the presence of urethritis when a gonococcal bacteria are not identifiable or the initial swab.

A typical case would be a male who presented to a GUM clinic with a purulent urethral discharge and dysuria.

A swab would be taken in clinic, microscopy performed which showed neutrophils but no Gram negative diplococci (i.e. no evidence of gonorrhoea). Clearly this patient requires immediate treatment prior to waiting for the Chlamydia test to come back and hence an initial diagnosis of NGU is made.

### Causative organisms include:

- Chlamydia trachomatis - most common cause
- Mycoplasma genitalium - thought to cause more symptoms than Chlamydia

### Management

- The treatment for NGU is **doxycycline 100 mg twice a day for seven days** or **Azithromycin 1 g stat**.
- Erythromycin is second line.

**NB: Gonococcal** urethritis has a **shorter** incubation period of 1 to 5 days on average and causes a **purulent** discharge.

**Treatment:** IM ceftriaxone, azithromycin, and fluoroquinolones.

**EX**: A 23-year-old man presents with a **one week** history of dysuria and penile discharge which he describes as **thin** and **colourless**. He last had **sexual** intercourse 2 weeks prior to the onset of symptoms.

A urethral swab demonstrates 10 PMN/HPF and no bacteraemia **>>> NGU.**

## Pelvic inflammatory disease (PID)

PID is a term used to describe infection and inflammation of the female pelvic organs including the uterus, fallopian

tubes, ovaries and the surrounding peritoneum.

It is usually the result of ascending infection from the endocervix.

## Causative organisms:

- **Chlamydia trachomatis** - the most common cause
- **Neisseria gonorrhoeae:** the 2nd common cause after Chlamydia.
- Mycoplasma genitalium
- Mycoplasma hominis

## Features:

- Lower abdominal pain
- Fever
- Deep dyspareunia
- Dysuria and menstrual irregularities may occur
- Vaginal or cervical discharge
- Cervical excitation

## Investigation:

- Screen for Chlamydia and Gonorrhoea.
- a pregnancy test should be done to exclude an ectopic pregnancy
- high vaginal swab
  - these are often negative

## Management:

- Due to the difficulty in making an accurate diagnosis, and the potential complications of untreated PID, consensus guidelines recommend **treatment once a diagnosis of PID is suspected**, rather than waiting for the results of endocervical swabs.
- **Oral ofloxacin + oral metronidazole.**
- **Or Ceftriaxone 500 mg IM STAT** followed by **oral doxycycline 100 mg BID + oral metronidazole 400 mg BD for 14 days.**
- RCOG guidelines suggest that in mild cases of PID intrauterine contraceptive devices may be left in.
- The more recent BASHH guidelines suggest that the evidence is limited but that ' Removal of the IUD should be considered and may be associated with better short term clinical outcomes

## Complications:

- perihepatitis (Fitz-Hugh Curtis Syndrome)
  - occurs in around 10% of cases
  - it is characterised by right upper quadrant pain and may be confused with cholecystitis
- infertility - the risk may be as high as 10-20% after a single episode
- chronic pelvic pain
- ectopic pregnancy

# Syphilis

- Syphilis is a sexually transmitted infection caused by the **spirochaete Treponema pallidum**.
- Infection is characterised by primary, secondary and tertiary stages.
- The incubation period is between **9-90 days.**

**Primary features:** It occurs **14 days to 3 months** post exposure:

- **Chancre - painless** ulcer at the site of sexual contact (genitalia).
- **Local painless lymphadenopathy**
- often not seen in women (the lesion may be on the cervix)

**EX**: A 25-year-old man presents with a **single, painless, indurated** ulcer on his penile shaft for **the past one week**. Several small, **painless**, inguinal lymph nodes were palpable bilaterally. His last unprotected sexual encounter was with a prostitute 3 weeks prior to presentation >>> **Chancre of 1ry Syphilis.**

**Diagnosis** of primary syphilis may be confirmed either with **dark field microscopy of secretions from the ulcer** or with **serology**.

**NB**: Bacterial culture of secretions from the ulcer is incorrect since Treponema pallidum **cannot** be **cultured** on routine bacterial culture media.

**Secondary features** - occurs **1-6 months** after primary infection:

- Systemic symptoms: **fevers**, painless generalized **lymphadenopathy**
- Generalized symmetrical **rash** on trunk, palms and soles
- **Buccal 'snail track' ulcers** (30%)
- **Condylomata lata.**

Classical palm lesions of secondary syphilis

More generalised rash of secondary syphilis

**Tertiary features (cardio-syphilis & Neuro-syphilis):** occurs up to **10-25 years** following the original inoculation.

- **Gummas**
- **Cardiovascular syphilis: AA** Aortic aneurysms, Aortic regurgitation and Aortitis.
- **Neurosyphilis:**
  - **GPI** (General paralysis of the insane): Gradual onset confusion, Hallucinations, Tremors, Fits, Cognitive impairment, Hyperreflexia, and Argyll-Robertson pupils.
  - **TD** Tabes dorsalis

**Features of congenital syphilis:**

- **Blunted upper incisor teeth**
- **Saddle nose**
- **deafness**
- Keratitis
- Saber shins

## Investigation:

T.P. is a very sensitive organism and cannot be grown on artificial media.

The diagnosis is therefore usually based on clinical features, serology and microscopic examination of infected tissue.

**Serological tests can be divided into:**

1) Cardiolipin tests (not treponeme specific): VDRL and RPR.
2) Treponemal specific antibody tests: TPHA.

**1) Cardiolipin tests:**

- Syphilis infection leads to the production of non-specific antibodies that react to Cardiolipin.
- Examples include **VDRL** (Venereal Disease Research Laboratory) & **RPR** (rapid plasma reagin)
- Insensitive in late syphilis
- **Becomes negative after treatment.**
- **Causes of false positive Cardiolipin tests:**
  - Pregnancy
  - SLE, anti-phospholipid syndrome
  - TB
  - HIV
  - Leprosy
  - Malaria

**2) Treponemal specific antibody tests:**

- Example: **TPHA** (Treponema pallidum Haem Agglutination test)
- **Remains positive all the life even after treatment**
- **The titre of TAPHA is meaningless and should not be done.**
- TPHA is positive for both syphilis and Yaws (caused by Treponema pertenue).

**Example of test results**

**Positive non-treponemal test + positive treponemal test**

- consistent with active syphilis infection

**Positive non-treponemal test + negative treponemal test**

- consistent with a false-positive syphilis result e.g. due to pregnancy or SLE (see list above)

**Negative non-treponemal test + positive treponemal test :**

- consistent with successfully treated syphilis

## Management:

- **Benzyl-penicillin long-acting 2.4 million units single IM injection.**
- Alternatives: **doxycycline**

**The Jarisch-Herxheimer reaction** is sometimes seen following treatment.

It occurs in up to **50**% of patients with **primary** syphilis, up to **90**% of patients with **secondary** syphilis, and 25% with early latent syphilis. It is very rare in late syphilis but may be dangerous if there are lesions around important anatomical sites (for example, sinoatrial node, larynx)

It start **within 12 hours** of the 1st dose of ttt and resolving within 24 hours.

It is usually not important in early syphilis unless there is neurological or ophthalmic involvement or in pregnancy when it may cause fetal distress and premature labour.

There will be **Fever, rash, hypotension, tachycardia** after **first** dose of antibiotic. It is thought to be due to the release of **endotoxins** following bacterial death and typically occurs **within a few hours of treatment.**

The reaction was originally described with **syphilis** treatment but is also well described in **rickettsial** diseases such as **Lyme** disease and **Q fever**.

A single dose of benzathine penicillin should cure most cases of **early syphilis**, thus **no further antibiotics should be necessary**.

## Q fever

- **Q fever is** a rickettsial zoonotic disease caused by **Coxiella burnetii.**
- **Q fever is** usually a **self-limited respiratory illness** due to the inhalation of infected aerosols, especially from animal products.

### Features

- typically prodrome: fever, malaise
- causes pyrexia of unknown origin
- transaminitis
- atypical pneumonia
- **endocarditis (culture-negative)**
- nausea, vomiting, diarrhoea, abdominal pain

Chronic infection may become established and can manifest as hepatitis, osteomyelitis or endocarditis.Endocarditis with **negative culture** findings and **seropositivity** is the main clinical presentation of **chronic Q fever**,

In **Q fever endocarditis**, the **aortic valve** is involved in over 80% of cases. A murmur is not always present, but augmentation of an existing murmur may occur. Low-grade fever (or no fever), signs of heart failure, hepatosplenomegaly, clubbing, arterial emboli, and leukocytoclastic vasculitic rash may also be present.

### Laboratory tests often show:

- Hepatitis
- **Anaemia**
- Elevated erythrocyte sedimentation rate
- **Thrombocytopenia** and
- Hypergammaglobulinaemia.
- Microscopic haematuria may be present.

The disease may be complicated by immune complex-mediated glomerulonephritis and arterial emboli.

**The diagnosis is best** made serologically and a phase I antibody titre to Coxiella burnetti (IgG and/or IgA) greater than 1:200 is virtually diagnostic of Q fever endocarditis.

### Management

- Most patients will recover within a few months with no treatment.
- **Doxycycline** is the treatment of choice for acute Q fever. OR prolonged courses of **tetracyclines**.

## Yaws

It is caused by **Treponema pertenue**, a **non-venereal treponemal** disease which is similar to syphilis may persist for many years.

**Neurological** involvement in Yaws is currently debated.

Serological testing is indistinguishable from that seen for syphilis, and differentiation is made on history and clinical picture.

Like syphilis, **penicillin** remains the drug of choice for ttt of Yaws, with erythromycin, tetracycline or doxycycline being possible alternatives.

Patients with Yaws, particularly where the infection is chronic, may require re-treatment every few years.

# Chancroid

It is a tropical disease caused by **haemophilus ducreyi.**

It is a **Gram negative rod** which is frequent cause of genital ulceration in Rwanda.

Chancroid is endemic in parts of the Caribbean basin, Africa and South West Asia, and is commoner in non-white uncircumcised populations.

The incubation period is **approximately one week**, following which erythematous **papules** develop on the external genitalia and surrounding regions. These later develop into **pustules** and may erode into sloughy haemorrhagic **ulcers**.

It causes single or multiple **painful** genital ulcers associated with **unilateral, painful** inguinal LN enlargement.

The ulcers typically have a sharply defined, ragged, **undermined** border.

Gram stain of ulcer exudate: "school of fish" collection of short, thick Gm -ve rods.

Definitive diagnosis is based on **culture using enriched chocolate agar**.

## Treatment

- Macrolides (**Azithromycin**) and **Quinolones**.

| Chancre | Chancroid |
|---|---|
| • Treponema pallidum<br>• **Painless**<br>• Hard indurated edge<br>• Non exudative<br>• Heal spontaneously within 3-6 wks. even if no ttt<br>• Can be in pharynx & genitalia | • haemophilus ducreyi<br>• **painful**<br>• **Soft**, ragged **edge**<br>• Grey or yellow purulent exudate |

## Summary of Genital Ulcers

- Genital herpes is most often caused by the herpes simplex virus (HSV) type 2 (cold sores are usually due to HSV type 1).
- Primary attacks are often severe and associated with fever whilst subsequent attacks are generally less severe and localised to one site. There is typically **multiple painful ulcers.**
- Syphilis is a sexually transmitted infection caused by the spirochaete *Treponema pallidum*.
- Infection is characterised by primary, secondary and tertiary stages.
- A painless ulcer (chancre) is seen in the primary stage. The incubation period= 9-90 days.
- Chancroid is a tropical disease caused by *Haemophilus ducreyi*. It causes painful genital ulcers associated with unilateral, painful inguinal lymph node enlargement.
- The ulcers typically have a sharply defined, ragged, undermined border.

**Lymphogranuloma venereum (LGV) is caused by *Chlamydia trachomatis*.**

**Typically infection comprises of three stages:**

- **Stage 1**: small **painless** pustule which later forms an ulcer
- **Stage 2: painful inguinal lymphadenopathy**
- **Stage 3: Proctocolitis**, the inflammation can be severe causing fistula and mimicking Crohn's disease.

**LGV is treated using doxycycline.**

### Other causes of genital ulcers

- Behcet's disease
- carcinoma
- granuloma inguinale: ***Klebsiella granulomatis****

*previously called *Calymmatobacterium granulomatis*

## Genital warts

Genital warts (also known as **condylomata accuminata**) are a common cause of attendance at genitourinary clinics.

They are caused by the many varieties of the human papilloma **virus HPV, especially types 6 & 11.**

It is now well established that HPV (primarily types **16, 18 & 33**) predisposes to **cervical cancer.**

### Features:

- Small (2 - 5 mm) fleshy protuberances which are slightly pigmented
- May bleed or itch

### Management of genital warts:

**1st line treatment:**

- Multiple, non-keratinised warts >> **Topical podophyllum**
- Solitary, keratinised warts >> **Cryotherapy**

**2nd line treatment:**

- **Imiquimod topical cream.**

Genital warts are often **resistant** to treatment and **recurrence** is common although the majority of anogenital infections with HPV clear without intervention within 1-2 years.

## Vaginal discharge

It is a common presenting symptom and is not always pathological.

### Common causes:

- Physiological
- Bacterial vaginosis
- Candida
- Trichomonas vaginalis

### Less common causes:

- Whilst cervical infections such as Chlamydia and Gonorrhoea can cause a vaginal discharge this is rarely the presenting symptoms.
- Ectropion.
- Foreign body.
- Cervical cancer.

**Key features of the common causes are listed below:**

| Condition | Key features |
|---|---|
| **B**acterial vaginosis (BV) (Gardnerella vaginalis) | • Offensive, thin, **white**/grey, **'fishy'** discharge. |
| **C**andida | • **'C**ottage **c**heese' discharge.<br>• Vulvitis.<br>• Itch. |
| Trichomonas vaginalis | • Offensive, yellow/green, frothy discharge.<br>• Vulvovaginitis.<br>• **Dyspareunia**<br>• **Dysuria.**<br>• **Strawberry** cervix. |

## Bacterial vaginosis (BV)

Bacterial vaginosis (BV) describes an overgrowth of predominately **anaerobic** organisms such as **Gardnerella vaginalis**.

This leads to a consequent fall in lactic acid producing aerobic lactobacilli resulting in a ↑ vaginal pH.

Douching, washing with scented soaps and gels (Dettol) have been implicated and the patient should be advised to stop these practices.

BV is the **commonest cause of abnormal vaginal discharge** in women of **childbearing** age. It is twice as common as vaginal candidiasis.

Whilst BV is not a sexually transmitted infection it is seen almost exclusively in sexually active women.

Bacterial vaginosis - overgrowth of predominately Gardnerella vaginalis

### Features:

- Vaginal discharge: **'fishy', offensive thin, milky white discharge which is not itchy.**
- **Asymptomatic in 50%**

**Amsel's criteria for diagnosis of BV:** 3 of the following 4 points should be present:

- Thin, white homogenous discharge.
- **Clue cells** on microscopy.
- ↑ Vaginal pH > 4.5
- Positive whiff test (addition of potassium hydroxide results in fishy odour)

## Management:

- **Oral metronidazole:** 500 mg twice daily given for 5-7 days, or alternatively, a single dose of oral metronidazole 2 g may be given.
- 70-80% initial cure rate.
- Relapse rate > 50% within 3 months.
- The BNF suggests **topical metronidazole** or **topical clindamycin** as alternatives.

## Bacterial vaginosis in pregnancy:

- Results in an increased risk of preterm labour, low birth weight and chorioamnionitis, late miscarriage.
- It was previously taught that oral metronidazole should be avoided in the first trimester and topical clindamycin used instead.
- Recent guidelines however recommend that **oral metronidazole is used throughout pregnancy.** The BNF still advises against the use of high dose metronidazole regimes.

| Bacterial vaginosis | | Trichomonas |
|---|---|---|
| | 'Offensive' vaginal dischage | Frothy, yellow-green discharge |
| Thin, white discharge | Vaginal pH > 4.5 | Vulvovaginitis |
| Microscopy: Clue cells | Treat with metronidazole | Strawberry cervix |
| | | Wet mount: motile trophozoites |

Comparison of bacterial vaginosis and *Trichomonas vaginalis*

**MRCPUK part 1 exam: H/O offensive vaginal discharge. Diagnosed as bacterial vaginosis. What is the most appropriate initial management?**
**>> Oral metronidazole**

# Trichomonas vaginalis

Trichomonas vaginalis is a highly motile, flagellated protozoan parasite. Trichomoniasis is a sexually transmitted infection (STI).

## Features

- vaginal discharge: offensive, yellow/green, frothy
- vulvovaginitis
- strawberry cervix
- pH > 4.5
- in men is usually asymptomatic but may cause urethritis

## Investigation

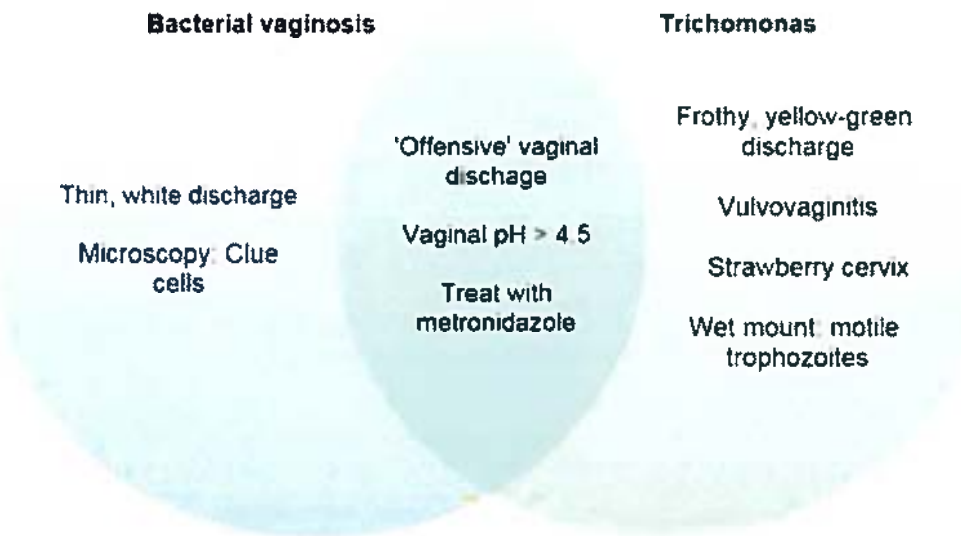
- microscopy of a wet mount shows motile trophozoites

## Management

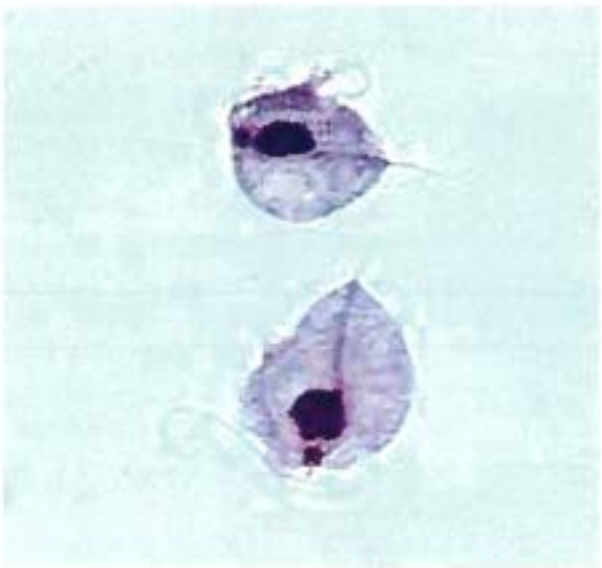
- oral metronidazole for 5-7 days, although the BNF also supports the use of a one-off dose of 2g metronidazole

**Sexual partners should also be treated**, as they may be **asymptomatic carriers.**

**Metronidazole** is relatively contraindicated in the first trimester of pregnancy and so treatment should be delayed until the second trimester.




Comparison of bacterial vaginosis and *Trichomonas vaginalis*



Trichomonas vaginalis - largely transparent core with finely granular eosinophilic cytoplasm. Surrounded by neutrophils with segmented nuclei

# Tropical Infections

## Malaria: Falciparum

### Clinical Feature of severe malaria:

- **Prostration:** generalized weakness so that the patient is unable to walk or sit up without assistance.
- **Temperature > 39 °C**
- **Impaired consciousness**
- **Multiple convulsions** > 2 episodes in 24 hours.
- **Respiratory distress**: acidotic breathing
- **Circulatory collapse or shock**: SBP < 70 mmHg.
- **Jaundice**
- **Haemoglobinuria**
- **Abnormal spontaneous bleeding**
- **Pulmonary oedema (CXR)**

### Laboratory finding of severe malaria:

- **Schizonts on a blood film**
- **Parasitaemia > 2%**
- **Severe anaemia:** Hb < **5** gm/dl
- **More than 1% of RBC infected.**
- **Hypoglycaemia:** < **2.2** mmol/L or < 40 mg/dl.
- **Metabolic acidosis:** HCO3 < 15 mmol/L
- **Hyperlactataemia:** Lactate > 5 mmol/L.
- **Renal impairment:** Creatinine > 265 Mmol/L
- **Complications** as below

### Complications:

- cerebral malaria: seizures, coma
- acute renal failure: blackwater fever, secondary to intravascular haemolysis, mechanism unknown
- acute respiratory distress syndrome (ARDS) (**Respiratory rate 30 per minute**)
- hypoglycaemia
- disseminated intravascular coagulation (DIC)

### Uncomplicated falciparum malaria:

- Strains resistant to chloroquine are prevalent in certain areas of Asia and Africa.

- The 2010 WHO guidelines recommend artemisinin-based combination therapies **(ACTs)** as first-line therapy
- Examples include artemether plus lumefantrine, artesunate plus amodiaquine, artesunate plus mefloquine, artesunate plus sulfadoxine-pyrimethamine, dihydroartemisinin plus piperaquine.
- Both artemether and atovaquone are not currently recommended in pregnancy.

## Severe falciparum malaria:

- **A parasite counts of more than 2%** will usually need **parenteral treatment irrespective** of clinical state.
- **IV Artesunate** is now recommended by **WHO** in preference to intravenous quinine.
- **If parasite count > 10%** then **exchange transfusion** should be considered.
- **Shock** may indicate **coexistent bacterial septicaemia** malaria rarely causes haemodynamic collapse.

**Severe falciparum** malaria >>> **Treatment**: **IV Artesunate or IV Quinine**

**Important notes:**

If one thick and thin film is negative, it should be repeated if the diagnosis is strongly suspected as **3 or more films are usually required to exclude malaria**.

**Hypoglycaemia** is an important side effect of **quinine** therapy and should be monitored in those having IV quinine.

**IV quinine** is reserved for **severe** or **cerebral malaria** (most deaths from M. falciparum occur in first 96 hours of starting treatment).

The initial dose should **NOT** be reduced in those patients severely ill with **renal** or **hepatic** impairment.

**Pregnancy is NOT a contraindication for quinine**

**WHO** Guidelines (**2006**) recommend:

-In the **first** trimester, both **Artesunate** and **quinine**.

-In the second and third trimester, **Artemisinins** are first line.

In severe malaria in pregnancy, any available treatment should be started without delay as both the mother and foetus' life are in danger.

It is as yet unclear exactly the role that the spleen plays in malaria parasites clearance, but case series suggest that **splenectomy** may be associated with **reduced** parasite **clearance** despite optimal anti-malarial therapy.

**EX**: Pt 30 yrs old has previous splenectomy dt RTA, and then after Asia trip he has hypotension, fever, low PLT, haemolysis >>> **Falciparum malaria**.

**EX**: 19 year old male from Zambia has **severe falciparum malaria**, renal impairment, **renal failure**, **massive haemolysis**, **black urine**, **anuria (Blackwater fever)** >>> **Treatment**: **IV Quinine** loading dose 20 mg/kg (up to maximum dose 1.4 gm) infused over 4 hours ± **haemodialysis.**.

## Malaria: non-falciparum

The most common cause of non-falciparum malaria is **Plasmodium vivax,** with Plasmodium **ovale** and Plasmodium **malariae** accounting for the other cases.

Plasmodium vivax is often found in Central America and the Indian Subcontinent whilst Plasmodium ovale typically comes from Africa.

### Features:

- General features of malaria: **fever,** headache, **splenomegaly.**
- Plasmodium vivax/ovale: **cyclical fever every 48 hours.**
- Plasmodium malariae: **cyclical fever every 72 hours.**
- Plasmodium malariae: is associated with nephrotic syndrome.

### Treatment:

- in areas which are known to be chloroquine-sensitive then WHO recommend either an **artemisinin-based combination therapy (ACT) or chloroquine**
- in areas which are known to be chloroquine-resistant an ACT should be used
- ACTs should be avoided in pregnant women
- patients with ovale or vivax malaria should be given primaquine following acute treatment with chloroquine to destroy liver hypnozoites and prevent relapse

**N.B:** Vivax and Ovale malaria have a hypnozoite stage and may therefore relapse following treatment.

**NB**: The **Duffy antigen** receptor on RBCs facilitates the entry of **P. vivax** into **the RBCs** and Duffy negative individuals are therefore resistant to this strain.

A similar situation exists with P. ovale but Duffy negative offers slightly less protection.

# Malaria: prophylaxis

There are around 1,500-2,000 cases each year of malaria in patients returning from endemic countries.

The majority of these cases (around 75%) are caused by the potentially fatal Plasmodium falciparum protozoa.

The majority of patients who develop malaria did not take prophylaxis.

**Prophylaxis does not give full protection.**

**Atovaquone + Proguanil combination** is given **1-2 days before** the travel and should be continued **7 days after return.**

It should also be remembered that UK citizens who originate from malaria endemic areas quickly lose their innate immunity.

| Drug | Side-effects + notes | Time to begin before travel | Time to end after travel |
|---|---|---|---|
| **Atovaquone + Proguanil (Malarone)** | **GI upset** | **1 - 2 days** | **7 days** |
| Chloroquine | Headache<br>Contraindicated in epilepsy<br>Taken weekly | 1 week | 4 weeks |
| **Doxycycline** | **Photosensitivity**<br>**Oesophagitis** | **1 - 2 days** | **4 weeks** |
| Mefloquine (Lariam) | Dizziness<br>Neuropsychiatric disturbance<br>**Contraindicated in epilepsy**<br>Taken weekly | 2 - 3 weeks | 4 weeks |
| Proguanil (Paludrine) | | 1 week | 4 weeks |
| Proguanil + chloroquine | See above | 1 week | 4 weeks |

In certain parts of South-East Asia there is widespread chloroquine resistance. Chemoprophylaxis using atovaquone + proguanil (Malarone), mefloquine (Lariam) or doxycycline is therefore recommended.

**Pregnant women** should be advised to avoid travelling to regions where malaria is endemic. Diagnosis can also be difficult as parasites may not be detectable in the blood film due to placental sequestration. However, if travel cannot be avoided:

- **Chloroquine** can be taken
- Proguanil: folate supplementation (5mg od) should be given
- Malarone (atovaquone + proguanil): the BNF advises to avoid these drugs unless essential. If taken then folate supplementation should be given
- Mefloquine: caution advised
- Doxycycline is contraindicated

It is again advisable to avoid travel to malaria endemic regions with **children** if avoidable. However, if travel is essential then children should take malarial prophylaxis as they are more at risk of serious complications.

- Diethyltoluamide **(DEET)** 20-50% can be used in children over 2 months of age.
- **Doxycycline** is only licensed in the UK for children **over** the age of 12 years.

- **Doxycycline** prophylaxis is the **safest** option with less resistance in many parts of the world compared to the other options available.
- Chloroquine prophylaxis has high levels of resistance to the drug around the world.
- Mefloquine prophylaxis is contradicted if the patient has a mental illness.

**MRCPUK part 1 exam: H/O vivax malaria treated initially with chloroquine then later given primaquine. What is the benefit of the primaquine?**

**>>> Destroy liver hypnozoites and prevent relapse**

**MRCPUK part 1 exam: A 25-year-old man with a history of epilepsy presents for advice regarding malarial prophylaxis. Next month he plans to travel to Vietnam. What is the most appropriate medication to prevent him developing malaria?**

**>>> Atovaquone + proguanil**

# Schistosomiasis

Schistosomiasis, or bilharzia, is a parasitic flatworm infection.
The following types of schistosomiasis are recognised:

- Schistosoma haematobium: urinary schistosomiasis.
- Schistosoma mansoni and Schistosoma intercalatum: intestinal schistosomiasis.
- Schistosoma **japonicum** is prevalent in **China**, Indonesia, Thailand and the Philippines mainly. It is the commonest cause of **Schistosoma encephalitis.** Its eggs are smaller unlike those of S. masoni and S. haematobium which are more likely to cause spinal cord schistosomiasis because of their larger size and spikes which do not enable them get to the brain hence the infection in the spinal cord.

## Schistosoma haematobium:

This typically presents as a **'swimmer's itch'** in patients who have recently returned from **Africa**,fever,urticaria,arthralgia,cough and diarrhoea.

Also occur in Middle East, Portugal, Spain and Greece.

Schistosoma haematobium is a risk factor for **squamous cell bladder cancer**.

## Features:

- Frequency
- Haematuria
- Haematospermia (occasionally)
- **Bladder calcification**
- It may progress to hydronephrosis and renal failure.

## Investigation

- for asymptomatic patients' serum schistosome antibodies are generally preferred
- for symptomatic patients the gold standard for diagnosis is urine or stool microscopy looking for eggs

## Management:

- Single oral dose of praziquantel.
- Praziquantel is not licensed for human use in the UK but is available on named patient basis.
- For S. haematobium and S. mansoni: **Praziquantel 40 mg/kg per day for 3 days** is recommended.
- For S. japonicum: **Praziquantel 60 mg/kg per day for 6 days** with a maximum dose of 5 grams per day **with prednisolone 1 mg/kg/day.**

**NB**: Since some of the pathology in **neuro-schistosomiasis** is secondary to **hypersensitivity** reactions there is need to use a **steroid**, in this case **prednisolone 1 mg/kg per day**. There is no consensus about when it should be started or stopped.

**N.B:**

- Schistosoma haematobium causes haematuria.
- Schistosomiasis is the most common cause of bladder calcification worldwide.
- Schistosomiasis is a risk factor for Squamous cell bladder cancer. (NOT Transitional cell carcinoma).

## Leishmaniasis

Leishmaniasis is caused by the intracellular protozoa Leishmania, usually being spread by sand flies.

The organism multiply in monocytes and macrophages, its incubation period may extend up to 10 years.

3 forms are seen: Cutaneous, mucocutaneous and visceral.

### Cutaneous leishmaniasis:

- Caused by Leishmania tropica or *Leishmania mexicana*
- Crusted lesion at site of bite
- May be underlying ulcer
- cutaneous leishmaniasis acquired in South or Central America merits treatment due to the risk of mucocutaneous leishmaniasis whereas disease acquired in Africa or India can be managed more conservatively

### Mucocutaneous leishmaniasis:

- Caused by **Leishmania brasiliensis**
- Skin lesions may spread to involve mucosae of nose, pharynx etc.

### Visceral leishmaniasis (Kala-azar):

- Mostly caused by **Leishmania donovani.**
- Occurs **Mediterranean**, Asia, South America, and Africa.
- The most common cause in **Southern Europe e.g. Turkey** is **Leishmania Infantum.**
- **Fever, night sweats**, rigors
- **Generalized lymphadenopathy.**
- **Massive splenomegaly.**

- Hepatomegaly
- Poor appetite, **weight loss.**
- Occasionally patients may report increased appetite with paradoxical weight loss.
- **Grey skin - 'kala-azar' it is an indian name which means darkening of the skin; black sickness or black fever.**

## Investigations

- pancytopenia secondary to hypersplenism
- There is also often marked polyclonal hypergammaglobulinemia.
- **Visualisation of the parasite (amastigote form) from lymph nodes, bone marrow or spleen is used as a confirmatory test.**
- PCR can be used to detect the parasite in the blood.
- Anti-leishmanial antibodies can be detected, but they remain positive up to several years after cure and therefore cannot be used to detect relapse.

## Treatment

- First line antimonials are sodium stibogluconate and meglumine antimoniate. Adverse effects influde cardiac arrhythmias and acute pancreatitis.
- Amphotericin B is increasingly being used.

## Treatment

Na stibogluconate is the mainstay of therapy, Amphotericin B is a possible alternative.

**EX:** Turkish male with fever, exhaustion, rash, dark skin, HSM and generalized lymphadenopathy **>>> Leishmania Infantum.**

Mucocutaneous ulceration following travel? **>>> Leishmania brasiliensis**

# Trypanosomiasis

- Two main form of this protozoal disease are recognised - African Trypanosomiasis (sleeping sickness) and American Trypanosomiasis (Chagas' disease)
- Two forms of **African trypanosomiasis**, or **sleeping sickness**, are seen - *Trypanosoma gambiense* in West Africa and *Trypanosoma rhodesiense* in East Africa. Both types are spread by the **tsetse fly.**
- *Trypanosoma rhodesiense* tends to follow a more acute course. Clinical

## Features:

- Trypanosoma chancre - painless SC nodule at site of infection.
- Intermittent fever.
- Enlargement of posterior cervical lymph nodes.
- Later: CNS involvement e.g. somnolence, headaches, mood changes, meningoencephalitis.

## Management:

- Early disease: **IV pentamidine** or **Suramin.**
- Later disease or central nervous system involvement: **IV Melarsoprol.**

**American trypanosomiasis**, or **Chagas' disease**, is caused by the protozoan *Trypanosoma cruzi*. The vast majority of patients (95%) are asymptomatic in the acute phase although a chagoma (an erythematous nodule at site of infection) and periorbital oedema are sometimes seen. Chronic Chagas' disease mainly affects the heart and gastrointestinal tract.

- **Heart**: **Myocarditis** may lead to **heart failure, RBBB**, arrhythmias and increased risk of **thromboembolism (DVT/PE).**
- **GIT** features: includes **megaoesophagus** and **megacolon** causing **dysphagia** and constipation.

Cardiac involvement is the leading cause of death in Pt with Chagas' disease.

### Management:

- Treatment is most effective in the **acute** phase using azole or nitroderivatives such as **Benznidazole** or **Nifurtimox.**
- Chronic disease management involves treating the complications e.g., heart failure.

# Tape worms

Tape worms are made up of repeated segments called proglottids.

These are often present in faeces and are useful diagnostically.

## Hydatid disease:

- Caused by the **Echinococcus granulosus (dog tapeworm).**
- Life-cycle involves dogs ingesting hydatid cysts from sheep liver.
- The adult worm is found normally in the dog and sheep intestine and man is an accidental intermediate host.
- The infection is seen in **Mediterranean areas**, East Africa, Australia and South America.
- Often seen in farmers.
- The **liver** is the commonest organ involved and may cause **liver cysts** >> pressure effect with **obstructive jaundice.**
- **Minor leaks** lead to increased pain and a mild allergic reaction characterised by flushing and urticaria.
- **Major rupture** can lead to a full-blown anaphylactic reaction in some cases.
- **CT abdomen** has an accuracy of 98% and the sensitivity to demonstrate the daughter cysts, it is the best test for the differentiation of hydatid from amoebic and pyogenic cysts in the liver.
- **Management**: **albendazole**

## Cysticercosis:

- Caused by **Taenia saginata (from beef)** and **Taenia solium (from pork).**
- It can affect either the **intestine**, causing an intestinal tapeworm infection, or the **CNS**, causing **neurocysticercosis** (seizures, CT brain shows periventricular cystic lesion in the parietal lobe with surrounding oedema).
- For confirming the diagnosis of neurocysticercosis:
  - Serum anticysticercal antibodies demonstrated by immunoblot assay.
  - CSF-ELIZA for detection of cysticercal antigens.
  - Resolution of intracranial cystic lesions after albendazole therapy.
  - Fundus examination for direct visualization of subretinal parasites.
- **Management**: **niclosamide**

# Nematodes

## Ancylostoma braziliense:

- **Most common cause of cutaneous larva migrans**
- Common in Central and Southern America
- **Management:**
  - The disease is self-limiting but the duration of disease varies considerably
  - Oral ivermectin in a single dose of 200 µg/kg body weight is the main treatment.
  - Other treatment options include oral albendazole or topical thiabendazole.

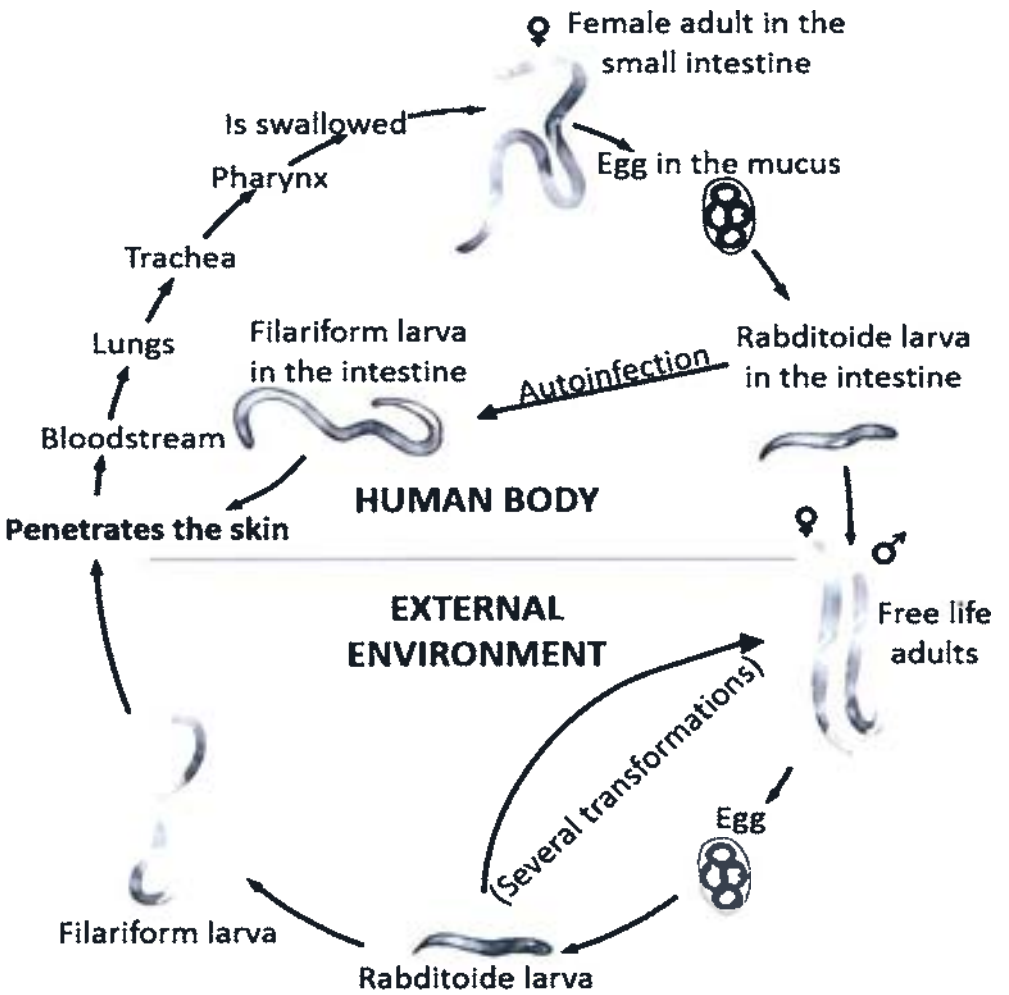
## Strongyloides stercoralis:

- Acquired percutaneously (e.g. walking barefoot).
- Causes pruritus and larva currens - this has a similar appearance to cutaneous larva migrans but moves through the skin at a far greater rate.
- Abdominal pain, diarrhoea, pneumonitis.
- Papulovesicular lesions where the skin has been penetrated by infective larvae e.g. soles of feet and buttocks.
- Larva currens: pruritic, **linear eryhthematous rash over groins and buttocks**.
- If the larvae migrate to the **lungs** a pneumonitis similar to Loeffler's syndrome may be triggered.
- May cause Gram negative septicaemia due carrying of bacteria into bloodstream.
- Eosinophilia sometimes seen.
- **Management:** thiabendazole, albendazole. Ivermectin also used, particularly in chronic infections.

If patient has chronic diarrhoea and has **both positive HIV and positive serology for strongyloides** >>> you should treat the **strongyloides** infection **firstly** with **Ivermectin** a short time before commencing **HAART** for the HIV.

## Toxocara canis:

- Commonly acquired by ingesting eggs from soil contaminated by dog faeces.
- **Commonest cause of visceral larva migrans.**
- Other features: eye granulomas, liver/lung involvement.




*Strongyloides stercoralis* **Life Cycle**, Nematode (Hookworm)

Diagram showing the lifecycle of *Strongyloides stercoralis*

# Helminths

## Nematodes (roundworms)

| Worm | Notes | Treatment |
|---|---|---|
| **Strongyloides stercoralis** | **Larvae** are present in soil and gain access to the body by penetrating the skin<br>**Features** include diarrhoea, abdominal pain, papulovesicular lesions where the skin has been penetrated by infective larvae e.g. soles of feet and buttocks, larva currens: pruritic, linear, urticarial rash, if the larvae migrate to the lungs a pneumonitis similar to Loeffler's syndrome may be triggered | Ivermectin and -bendazoles are used |
| **Enterobius vermicularis** (pinworm) | Threadworm infestation is asymptomatic in around 90% of cases, possible<br>**features** include perianal itching, particularly at night; girls may have vulval symptoms<br>**Diagnosis** may be made by the applying sticky plastic tape to the perianal area and sending it to the laboratory for microscopy to see the eggs | **- bendazoles** |
| Ancylostoma duodenale, Necator americanus (hookworms) | Larvae penetrate skin of feet; gastrointestinal infection → anaemia<br>Thin-shelled ova | - bendazoles |
| **Loa loa** | Transmission by deer fly and mango fly<br>**Causes** red itchy swellings below the skin called 'Calabar swellings', may be observed when crossing conjunctivae | Diethylcarbamazine |

| Worm | Notes | Treatment |
|---|---|---|
| **Trichinella spiralis** | Typically develops **after eating raw pork**<br>Features include fever, **periorbital oedema** and **myositis** (larvae encyst in muscle) | - bendazoles |
| Onchocerca volvulus | Causes 'river blindness'. Spread by female blackflies<br>**Features** include blindness, hyperpigmented skin and possible allergic reaction to microfilaria | Ivermectin<br>r**IVER**blindness<br>= **IVER**mectin |
| Wuchereria bancrofti | Transmission by female mosquito<br>**Causes** blockage of lymphatics → elephantiasis | Diethylcarbamazine |
| **Toxocara canis** (dog roundworm) | Transmitted through ingestion of infective eggs.<br>**Features** include visceral larva migrans and retinal granulomas<br>**VISCious dogs → blindness** | Diethylcarbamazine |
| **Ascaris lumbricoides** (giant roundworm) | • the most common nematode parasite of humans.<br>• Eggs are visible in faeces<br>• large roundworm, growing up to 35 cm in length<br>• result of pneumonitis caused by the worm's migration through the lungs<br>• May cause intestinal obstruction and occasional migrate to lung (Loffler's syndrome)<br>• biliary/pancreatic duct obstruction | -- bendazoles<br>**Piperazine is the treatment of choice in patients presenting with bowel obstruction;** **mebendazole** may be used to treat other infections. |

## Cestodes (tapeworms)

| Worm | Notes | Treatment |
|---|---|---|
| **Echinococcus granulosus** | • Responsible for **hydatid disease**<br>• Transmission through **ingestion of eggs in dog faeces.**<br>• Definite host is dog, which ingests hydatid cysts from sheep, who act as an intermediate host.<br>• **Often seen in farmers.**<br>**Features** include **liver cysts** and **anaphylaxis if cyst ruptures** (e.g. during surgical removal)<br>• **the most appropriate next step in diagnosis?**<br>○ **ELISA testing for Echinococcus** | -bendazoles |
| Taenia solium | Often transmitted after eating undercooked pork.<br>**Causes** cysticercosis and neurocysticercosis, mass lesions in the brain 'swiss cheese appearance' | -bendazoles |
| Fasciola hepatica (the liver fluke) | May cause biliary obstruction | Triclabendazole |

## Trematodes (flukes)

| Worm | Notes | Treatment |
|---|---|---|
| Schistosoma haematobium | Hosted by snails, which release cercariae that penetrate skin.<br>**Causes** 'swimmer's itch' - frequency, haematuria. Risk factor for squamous cell bladder cancer | Praziquantel |
| **Paragonimus westermani** | **Caused** by undercooked crabmeat, results in **secondary** bacterial infection of lungs | Praziquantel |
| **Clonorchis sinensis** | **Caused** by undercooked fish<br>**Features** include biliary tract inflammation.<br>**Known risk factor for cholangiocarcinoma** | Praziquantel |

## Giardiasis

Giardiasis is caused by the flagellate protozoan **Giardia lamblia**. It is spread by the faeco-oral route.

### Features:

- **Often asymptomatic**
- Lethargy, **bloating**, abdominal pain
- **Non-bloody diarrhoea**
- **Chronic diarrhoea**, malabsorption and lactose intolerance can occur
- **Stool** microscopy for trophozoite and cysts are classically **negative**, therefore **duodenal fluid aspirates or 'string tests'** (fluid absorbed onto swallowed string) are sometimes needed.

### Investigations

- stool microscopy for trophozoite and cysts: sensitivity of around 65%
- stool antigen detection assay: greater sensitivity and faster turn-around time than conventional stool microscopy methods
- PCR assays are also being developed

### Treatment:

- **Metronidazole.**

## Cholera

It is caused by Vibrio cholerae - Gram negative bacteria.

### Overview

- caused by Vibro cholerae - Gram negative bacteria
- Because the organism is not acid-resistant, it **depends on its large inoculum size** ( infectious dose) to **withstand gastric acidity.**
  - If ingested with water, a higher infectious dose is needed. When ingested with food, fewer organisms are required to produce disease.
  - ↓ gastric acidity (anti-acid drugs, gastrectomy) >> ↑risk of cholera infection and severity

## Mechanism by which cholera leads to fluid loss:

**Cholera toxin has two parts, A and B.**

- B subunits are responsible for binding to a ganglioside (monosialosyl ganglioside, **GM1 receptor**) located on the surface of the cells that line the intestinal mucosa.
- B binds while A activates **G protein** >> **activates adenylate cyclase** >> **↑(cAMP)** >> unrestricted chloride secretion from villous **crypts**.

**cholera toxin stimulates the generation of cyclic AMP as the second messenger**

## Features:

- **Profuse 'rice water' diarrhoea**
- Dehydration
- Hypoglycaemia

## Management:

- Oral rehydration therapy
- Antibiotics: **doxycycline**, **ciprofloxacin.**

"Individuals with blood group **O** are more susceptible than other individuals to severe cholera, although the mechanism is unknown."

# Special Diagnoses

## Pyrexia of unknown origin (PUO)

Prolonged fever of **> 3 weeks** which **resists diagnosis after a week in hospital**.

**1) Neoplasia:**

- **Preleukaemia**
- **Lymphoma**
- **Hypernephroma**
- **Atrial myxoma**

**2) Infections:**

- Abscess
- TB

**3) Connective tissue disorders:**

## Lymphadenopathy (causes of generalised lymphadenopathy)

**Infective:**

- EBV (Infectious mononucleosis)
- HIV, including seroconversion illness
- Eczema with secondary infection
- Toxoplasmosis
- Rubella
- **CMV**
- T.B
- Roseola infantum

**Neoplastic:** Leukaemia & Lymphoma

**Others**

- Autoimmune conditions: SLE, rheumatoid arthritis
- Sarcoidosis
- GVHS
- **Drugs: phenytoin and to a lesser extent allopurinol, isoniazid**

**N.B:** Kawasaki disease causes only cervical lymphadenopathy

## African Tick Typhus

It is caused by Rickettsiae

### Features:

- Hx of tick bites
- **Black spots** on forearm/thigh
- Low grade fever
- Faint maculopapular rash

**Treatment:** **Doxycycline 100 mg single dose** leads to rapid clinical recovery.

## Rocky Mountain spotted fever (RMSF)

It is the most lethal and most frequently reported rickettsial infection, spread by **ticks**, common in **USA**.

**It is caused by Rickettsia rickettsii.**

Physicians must maintain a high index of suspicion for RMSF in patients who are febrile as it is essentially a clinical diagnosis.

Patients with **unexplained febrile illness**, even if they have no history of a tick bite or travel to an endemic area but have **palms & soles rash and myalgia** should be suspected to RMSF.

Rash **is a major diagnostic sign**, the maculopapular rash usually appears **2-6 days after onset of fever** and progresses through stages and distributions that are never pathognomonic, the rash begins on the wrists (**palms**) and ankles (**soles**) and spreads centripetally to involve the trunk and extremities, later the rash becomes petechial in 50% of patients.

### Features:

- Fever
- Rash on hands, feet which later >>> desquamate (peel)
- Tachycardia with **NO HYPOTENSION** (unlike Staph Toxic Shock Syndrome)
- Sometimes, **leukopenia** and **thrombocytopenia.**

### Treatment

**Doxycycline is the drug of choice** for adults and children and is almost always curative, especially if given in the first 5 days of illness.

- Tetracyclines acts on 30S ribosomes to prevent protein synthesis in the infecting organism.
- **Aluminium hydroxide can complex with this antibiotic in the gastrointestinal tract, preventing absorption.** Dairy products ingested at the same time can also cause this.
- **Aluminium hydroxide medication should be stoped till the antibiotic course is finished**

## Mediterranean Spotted Fever (Boutonneuse fever)

It is a fever caused by the Rickettsia conorii and transmitted by the dog tick Rhipicephalus sanguineus.

### Features:

- Incubation period: 7 days
- It manifests abruptly with **high fevers**, **chills**, **myalgia**, joint pain **severe headache**, photophobia and diarrhea.
- The location of the bite forms a **black spots or ulcerous crust** (tache noire).
- Around the 4$^{th}$ day of the illness an **exanthema (widespread rash)** appears, first macular then maculopapular and sometimes petechial.

**Treatment: Doxycycline.**

## Dengue fever

Dengue fever is a **viral** infection which can progress to **viral haemorrhagic fever** (also **yellow fever**, Lassa fever, **Ebola**).

### Basics:

- dengue virus is a RNA virus of the genus Flavivirus
- Transmitted (carried) by the **Aedes aegypti mosquito** in endemic areas as **South East Asia (Indonesia)** and **North Australia**.
- There are 4 serotypes.
- Incubation period of 7 days.
- The patient often experiences a sudden onset of fever, headache, and retro-orbital pain and back pains with severe myalgia hence the name **break bone fever.**
- A form of **disseminated intravascular coagulation (DIC)** known as **dengue haemorrhagic fever (DHF)** may develop: clotting abnormalities and a bleeding diathesis.
- Around 20-30% of these patients go on to develop **dengue shock syndrome (DSS).**

### Features:

- **Severe fever** up to 40.
- **Severe headache** (often **retro-orbital & frontal**)
- **Generalized maculopapular rash: palatal vesicles** and **sclera injection**
- **Facial flushing (dengue)**
- **myalgia, bone pain and arthralgia ('break-bone fever')**
- Pleuritic pain
- **Low TLC & Low platelet count in 50% of patients.**
- **Raised transaminase level (ALT).**
- **Low Na.**

### Treatment:

- Treatment is entirely **supportive (symptomatic)** e.g. **fluid resuscitation (Normal Saline)** and **pain relief.**
- But other patients who develop thrombocytopenia and bleeding diathesis may require blood transfusion, and correction of clotting etc.
- (Corticosteroids have NO role).

## Yellow fever

Type of viral haemorrhagic fever (also dengue fever, Lassa fever, Ebola).

### Basics

- zoonotic infection: spread by *Aedes* mosquitos
- incubation period = 2 - 14 days

### Features

- may cause mild flu-like illness lasting less than one week
- **classic description involves sudden onset of high fever, rigors, nausea & vomiting. Bradycardia may develop. A brief remission is followed by jaundice, haematemesis, oliguria**
- if severe jaundice, haematemesis may occur
- Councilman bodies (inclusion bodies) may be seen in the hepatocytes

## Babesiosis

It is a **tick**-borne **malaria-like illness** caused by species of the intraerythrocytic protozoan **Babesia**.
Babesiosis is a **clinical diagnosis**.
Patients present with similar symptoms to malaria i.e. fever, chills and rigors.
The intraerythrocytic Babesia destroy the RBCs causing **hemolytic anaemia** and **haemoglobinuria** with secondary reactive **polyclonal hypergammaglobulinaemia.**
Symptoms are greater with a higher percentage of parasitism.
Babesiosis is frequent in endemic areas of the **USA**, particularly Long Island, New York, Nantucket Martha's Vineyard and Massachusetts.
Patients without a spleen have a more fulminant and prolonged clinical course and may have overwhelming infection and a fatal outcome.

## Congenital infections (e.g. rubella, toxoplasmosis and cytomegalovirus)

**Cytomegalovirus is the most common congenital infection in the UK.** Maternal infection is usually asymptomatic.

| | Rubella | Toxoplasmosis | CMV |
|---|---|---|---|
| Characteristic features | • **Sensorineural deafness.**<br>• **Congenital cataracts.**<br>• Glaucoma.<br>• Congenital heart disease (e.g. PDA). | • **Cerebral calcification.**<br>• **Chorioretinitis**<br>.<br>• Hydrocephalus. | • Growth retardation.<br>• Purpuric skin lesions. |
| Other features | • Growth retardation.<br>• **HSM.**<br>• Purpuric skin lesions.<br>• **'Salt and pepper' chorioretinitis.**<br>• Microphthalmia.<br>• Cerebral palsy. | • Anaemia.<br>• **HSM.**<br>• Cerebral palsy. | • Sensorineural deafness.<br>• Encephalitis<br>• Seizures.<br>• Pneumonitis.<br>• **HSM.**<br>• Anaemia.<br>• Jaundice.<br>• Cerebral palsy. |

**Congenital rubella**:
- Sensorineural deafness
- Congenital cataracts

**Congenital toxoplasmosis:**
- Cerebral calcification
- Chorioretinitis

**NB: Chorioretinitis** is found in around 75% of patients with **congenital toxoplasmosis**.

**NB:** A form of **'salt and pepper' chorioretinitis** is also seen in **congenital rubella** but this is not a common feature.

**NB**: A **positive rubella haemagglutination inhibition (HAI)** combined with a **negative rubella IgM** is consistent with:
1) Early acute infection with rubella
2) Previous vaccination, or
3) Previous rubella infection.

The rubella IgM may take several days to rise and the test should be repeated one to two weeks later.

**EX**: A 24-year-old woman consults her GP with a **one day history** of **fever** and a **macular rash.** She is 8 weeks pregnant and has not been immunised against rubella.
Lab: negative rubella IgM and a rubella haemagglutination inhibition (HAI) titre of 1:64.
What advice do you give the patient >>> **Repeat rubella IgM after 1-2 wks**.

# Post-exposure prophylaxis

## Hepatitis A:

- Human Normal Immunoglobulin (HNIG) or hepatitis A vaccine may be used depending on the clinical situation.

## Hepatitis B:

- **HBsAg positive source:**
  - If the person exposed is a known responder to HBV vaccine then **a booster dose should be given.**
  - If they are in the process of being vaccinated or are a non-responder they need to have **hepatitis B immune globulin (HBIG) and the vaccine.**
- **Unknown source:**
  - For known responders the green book advises considering a booster dose of HBV vaccine.
  - For known non-responders HBIG + vaccine should be given whilst those in the process of being vaccinated should have an accelerated course of HBV vaccine.

## Hepatitis C:

- **Monthly PCR**
- If seroconversion >>> then interferon +/- ribavirin

## HIV:

- **A combination of oral antiretrovirals** (e.g. Tenofovir, emtricitabine, lopinavir and ritonavir) **as soon as possible** (i.e. within 1-2 hours, but may be started **up to 72 hours** following exposure) **for 4 weeks.**
- **Serological testing at 12 weeks** following completion of post-exposure prophylaxis.
- Reduces risk of transmission by **80%.**

Post-exposure prophylaxis for HIV: oral antiretroviral therapy ASAP for 4 weeks

## Varicella zoster:

- **VZIG** for **IgG negative pregnant women/immunosuppressed**.

**Estimation of transmission risk for single needle stick injury:**

| Virus | Change of transmission |
|---|---|
| Hepatitis B | **20-30%** |
| Hepatitis C | **0.5-2%** |
| HIV | **0.3%** |

## Whooping cough (pertussis)

It is caused by the bacterium **Bordetella pertussis**.

B. pertussis is a very small gram-negative aerobic coccobacillus that appears singly or in pairs.

Infection is characterised by paroxysms of coughing. **Lymphocytosis** is typically found.

The pertussis vaccine is estimated to be 63% to 94% effective in the diphtheria-pertussis-tetanus (DPT) shot. A **rare** complication is a **hemiseizure-hemiplegia syndrome**, which is thought to be related to **post-immunisation hyperthermia** rather than direct neurological toxicity.

The incidence of pertussis is highest in **infants**, but it is also seen in **adolescents** and **adults**.

It is **infants under the age of 3 months** who are at the **highest risk** of severe complications, hospitalisation and death.

It is associated with **febrile convulsions** which are seen with **equal prevalence** to other childhood infectious diseases.

Although it is a bacterial disease, **antibiotics do not alter** the clinical course once the disease is established. Erythromycin, clarithromycin and azithromycin may be given however as they have been shown to reduce the period the patient is infective for.

## Botulism

**It is caused** by toxigenic strains of Clostridium botulinum and is usually caught from improperly tinned food, although it can also be contracted from **meat products** and **uncooked seafood**, and from **injecting abscesses**

**It causes diplopia, blurred vision, photophobia, bulbar palsy, ataxia** and **sudden** cardiorespiratory failure with **no GI symptoms.**

patient usually fully conscious with no sensory disturbance

The patient should be admitted at **ITU** and **intubated** early. **Antitoxin** needs to be given as quickly as possible before the patient has a cardiac arrest.

**Botulism is** usually diagnosed via **stool culture**.

# Encephalitis

## Encephalitis may be caused by:

1) **Direct invasion** by a neurotoxic virus (encephalitis): caused by enteral viruses, HSV 1 and 2, varicella, CMV, EBV, respiratory viruses, human herpes virus 6 (HHV6), rubella or mumps.
2) **Post-infectious encephalopathy**: delayed brain swelling because of an immunological response to the antigen, i.e. a **neuroimmunological response,** caused by **measles** or **varicella zoster** (cerebellar ataxia).
3) Slow virus infection, for example, HIV or **subacute sclerosing pan encephalitis (SSPE).**

## Diagnosis

- Although CT or MRI scan of the head should be performed, it cannot give a specific diagnosis. HSV has a predilection for involvement of the temporal lobes, which can sometimes be seen on CT.
- A lumbar puncture is the key to the diagnosis.
- PCR (polymerase chain reaction) for HSV has a 98% sensitivity and >95% specificity, making it at least equal to the biopsy.

## Treatment

- HSV encephalitis is best treated with IV acyclovir.
- Acyclovir-resistant herpes is treated with foscarnet

# Histoplasmosis

It is caused by **Histoplasma capsulatum**, a dimorphic soil **fungus**.

It is a yeast type fungus which is endemic in **Southern USA** at Mississippi, Ohio and Missouri, it occurs particularly in areas which house large **bat** and **bird** populations.

Slowly progressing chronic form occurs in those who are fit and **immunocompetent**.

Those who are weak, very young or very old or **immunocompromised** tend to acquire a disseminated infection.

**Acute** infection causes glandular fever-type symptoms, malaise, anorexia, arthralgia, headache and **erythema nodosum**. It can cause a **TB-like illness**

with cough, haemoptysis, dyspnoea and **BHL** with **cavitary** lesions by CXR. Sometimes **hepatitis** is associated.

**Disseminated** infection causes bilateral adrenal enlargement in 80% of cases and it can result in adrenal insufficiency.

**Diagnosis**: **Adrenal biopsy or FNA** with **Groccott stain (Groccott-stained adrenal biopsy).**

## Investigation

- Chest X-ray often reveals a solitary lung lesion.
- Disseminated histoplasmosis can cause systemic granulomatous inflammation and cavitation, which may be fatal.
- The organisms can be visualized using methenamine silver or periodic acid-Schiff staining.
- **On histology >>> *Macrophages containing yeast***
  - Histoplasma capsulatum is a small intracellular yeast that is phagocytosed by alveolar macrophages.

**Treatment: Itraconazole for 3-6 months.**

**NB**: DD of **FUO (Fever of unknown origin)** and **bilateral adrenal swelling** is: **TB**, **Lymphoma** or **Histoplasmosis**.

**EX**: Pt 50 years old with FUO for 3 months with night sweat and weight loss, Abdominal CT shows bilateral adrenal swelling? **>> Histoplasmosis >>> Groccott-stained adrenal biopsy.**

## Swimmer's ear

C/O: severe otitis externa, earache, discharge and spreading superficial skin infection with history of swimming in the **hotel pool**.

It is caused by **Pseudomonas aeruginosa**.

So, it is **not responding to Augmentin.**

More severe spreading infections occurs more commonly in **diabetic** cases.

**Treatment**: local and systemic antibiotics with ENT surgeon consultation.

**NB**: **Persistent pyrexia 3 days after** commencing powerful broad spectrum antibiotics (Meronem+ Garamycin + Teicoplanin) raises the possibility of **fungal** infection like systemic candidiasis and aspergillosis >>> so add **Amphotericin B** (its liposomal form is less nephrotoxic).

**Oropharyngeal candidiasis** may be treated with **topical antifungal** agents (such as nystatin, clotrimazole, and amphotericin B oral suspension/lozenges).

**Oesophageal candidiasis** requires **oral or IV therapy** (usually with **Fluconazole** or Itraconazole for at least **14-21 days**) as topical therapy is inadequate.

# EL MAGRABY & SHERIF'S

# STEP UP to MRCP

## Review Note For Part I & Part II

3rd Edition

- The freshly revised and updated edition of STEP UP TO MRCP- who continued to be the reliable source for medicine - is the go-to source for current data and recommendations on diagnosis and patient management of all aspects of medicine, necessary to pass- not only MRCP, MRCPI, Masters, MDs and Board exams -but also ensure successful and safe daily practice.

- In a world of rapidly changing information and guidelines, this edition was published in response to increasing demand for a source that can successfully walk the line between the data overflow and over simplification, and I think this book did so.

- This edition includes latest and best guidelines up to those published in 2023 from NICE, ASC, AHA, RCP, AURAL, KDIGO, GOLD and other reputable and first ranked societies. It is also highly illustrated with diagrams, photos and tables that almost present in every page of this book.

- Whether you need a quick, easy and reliable source or you prepare to set for national or international exam, this comprehensive source will be your essential aid.

El Marwa publishing and distribution

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ISBN 978-977-86708-2-0

9 789778 670820

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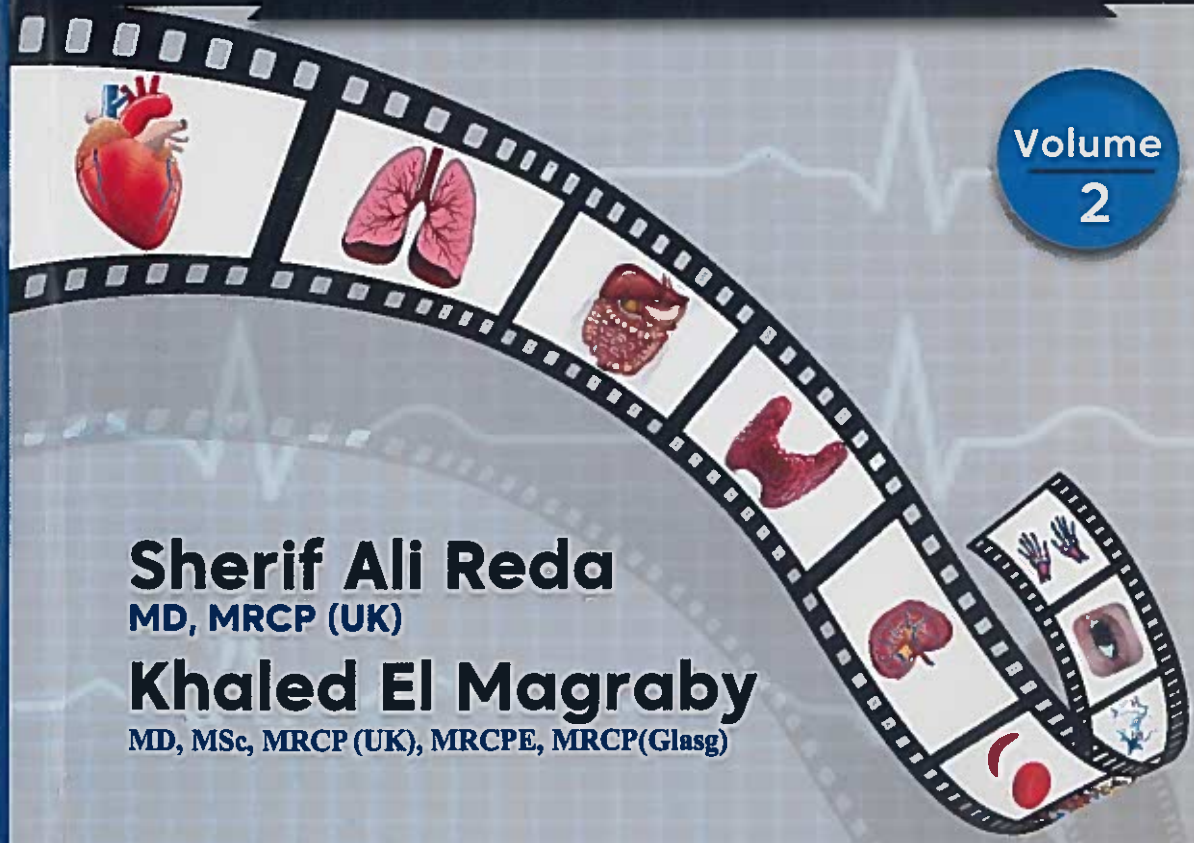
3rd Edition

# STEP UP to MRCP

Review Note For Part I & Part II



Volume 2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VOLUME 2

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MIDDLE EAST FOR PUBLISHING & DISTRIBUTION

El MARWA publishing and distribution

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**ISBN: 978-977- 86708-2-0**
Deposit Number: 11303/2023

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**Publisher**: Middle East & El Marwa for Publishing & Distribution
Cairo, Egypt
Tel. (+20) 1110150022 – (+20) 1211161255
E-mail: ar201078@gmail.com
Publishing Services Manager & Design: Abd El Hamid Abd El Ghafar
Printing Services Manager: Abd El Aleem Adel El Syed
Printed in Egypt

# PREFACE

I feel fortunate and honored to present this third edition of STEP UP TO MRCP to the community of medicine.it has been 7 years since the first edition of this book; the long interval and the increasing demand for new edition of this book- who gained a lot of trust and credibility of the medical society- was the main challenge to publish this edition.

The other challenge was to walk the line between over simplification and data overflow, in the world of internal medicine which is full of guidelines and studies.

this was the main stimulus to fill this book with diagrams, illustrations, photos, radiology material and tables, as to make it easy for everyone to pick up the needed information in an easy way for new and experienced physicians as well.

I would like to thank god for helping me to accomplish this work, and also I would like to thank the god father of this book Khalid Maghraby who invited me to contribute to this edition and helped us during completing this work.

My deepest gratitude goes to my wife Shaimaa and my kids Nada and Mohamed who tolerated me throughout this hard time. to my mother who continued to inspire and pray for me and finally to the soul of my father.

Last but not least, I would like to thank Mr,Abdelhamid the publisher and owner of middle east library ,who spent a lot of time and effort to make this book exists, attractive and in such a wonderful quality.

**S.A. Reda, MD, MRCP (UK)**
June 2023

# FORWARD

Welcome to the world of internal medicine! This medical book is the result of great effort and dedication by its author to provide you with the most updated and comprehensive knowledge of internal medicine.

The book is designed to meet the needs of every medical student, resident, and physician who is pursuing a career in internal medicine. It covers the whole spectrum of internal medicine, from the basics of pathophysiology to the most advanced treatment strategies.

The book is structured in a clear and well-organized manner.

This book is highly recommended for everyone studying internal medicine, particularly those aiming to obtain the MRCP degree. It is an invaluable resource that will help you build a strong foundation in internal medicine and prepare you for success in your medical career.

**Prof. Dr. Khaled Makboul**
Professor of internal medicine and endocrinolgy
Ain Shams University
June 2023

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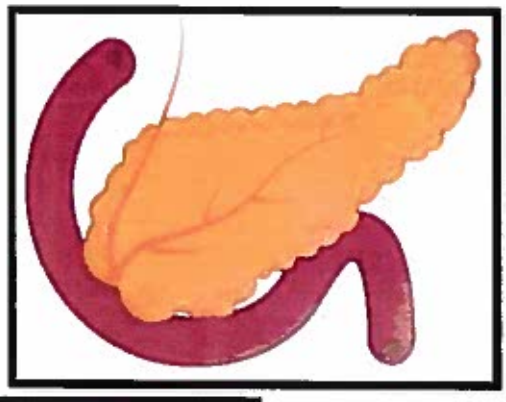
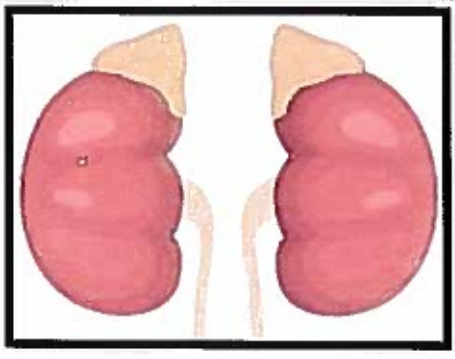
# Endocrinology





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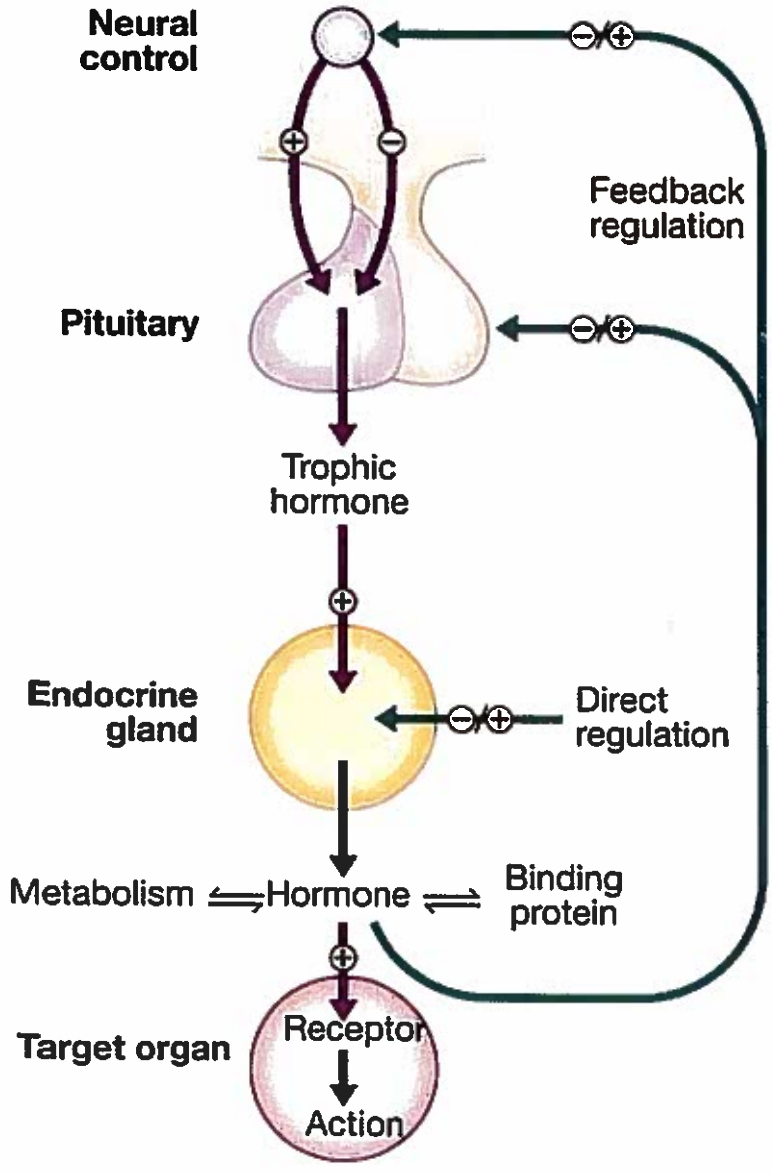
# PITUITARY DISORDERS

## Anatomy and physiology




An archetypal endocrine axis. Regulation by negative feedback and direct control is shown, along with the equilibrium between active circulating free hormone and bound or metabolized hormone.

## Insulin stress test

### Basics:

- Used in investigation of **hypopituitarism**
- IV insulin given, GH and cortisol levels measured.
- With normal pituitary function GH and cortisol should rise.
- Insulin stress tests are also occasionally **used to differentiate Cushing's from pseudo-Cushing.**

### Contraindications:

- Epilepsy
- Ischaemic heart disease
- Adrenal insufficiency

## Dynamic pituitary function tests

A dynamic pituitary function test is used to assess patients with **suspected primary pituitary dysfunction.**
**Insulin, TRH** and **LHRH** are given to the patient following which >>>>>>>>>>>>>> the serum **glucose, cortisol, GH, TSH, LH** and **FSH** levels are recorded at regular intervals. **Prolactin** levels are also sometimes measured*
A normal dynamic pituitary function test has the following characteristics:

- GH level rises > 20mu/l
- Cortisol level rises > 550 mmol/l
- TSH level rises by > 2 mu/l from baseline level
- LH and FSH should double

Dopamine antagonist tests using metoclopramide may also be used in the investigation of hyperprolactinaemia. A normal response is at least a twofold rise in prolactin. A blunted prolactin response suggests a prolactinoma.

## Pituitary adenoma

A pituitary adenoma is a benign tumour of the pituitary gland. They are common (10% of all people[1]) but in most cases will never be found (asymptomatic) or are found as an incidental finding. They account for around 10% of adult brain tumours.
Prolactinomas are the most common type and they produce an excess of prolactin. After prolactinomas, non-secreting adenomas are the next most common, then GH secreting and then ACTH secreting adenomas.

## Classifications

### According to size:

- Microadenoma: ≤ 10 mm
- Macroadenoma: > 10 mm

### According to hormone secretion

- **Secretory pituitary adenomas (60%): hormone secretion >> hyperpituitarism**
  - Lactotroph adenoma: Prolactinoma 35-40%.
  - Somatroph adenoma: Growth hormone (acromegaly) 10-15%.
  - Corticotroph: ACTH adenoma (Cushing's disease) 5-10%.
  - Thyrotroph: TSH adenoma <5%
- **Non-secretory pituitary adenomas 'chromophobe'**: Non-functioning 30-35%.
  - **Which nonfunctioning pituitary adenoma subtype is characterized by a high recurrence rate, invasion, and increased risk of hemorrhagic infarction?**
- **Corticotroph adenoma**

## Features

depends on the tumor **size** and whether the tumor **produces** hormones

- **Secretory microadenomas** >> hyperpituitarism according to which hormone is secreted
- **Secretory macroadenomas** >> hyperpituitarism + **mass effects** (e.g., headache, **bitemporal hemianopsia,** diplopia)
- **Non-secretory microadenomas >> Asymptomatic**
- **Non-secretory macroadenomas >> Hypopituitarism + mass effects** (e.g., headache, bitemporal hemianopsia, diplopia)

### Mass effects

- Superior extension >> firstly compression of the optic apparatus and later the hypothalamus.
- Lateral extension >> compression or invasion of the cavernous sinus can compromise third, fourth, or sixth cranial nerve functions, manifest as diplopia in 5 to 15% of pituitary tumour patients.

## Pituitary adenomas typically cause symptoms by:

- excess of a hormone (e.g. Cushing's disease due to excess ACTH, acromegaly due to excess GH or amenorrhea and galactorrhea due to excess prolactin)
- depletion of a hormone(s) (due to compression of the normal functioning pituitary gland)
  - **non-functioning tumours, therefore, present with generalised hypopituitarism**

- stretching of the dura within/around pituitary fossa (causing headaches)
- compression of the optic chiasm (causing a bitemporal hemianopia due to crossing nasal fibers)

Alternatively, pituitary adenomas, particularly microadenomas, can be an incidental finding on neuroimaging and therefore called a 'pituitary incidentaloma'.

## Investigation requires:

- a pituitary blood profile (including: GH, prolactin, ACTH, FH, LSH and TFTs)
- formal visual field testing
- MRI brain with contrast

## Differential diagnoses include:

- pituitary hyperplasia
- craniopharyngioma
- meningioma
- brain metastases
- lymphoma
- hypophysitis
- vascular malformation (e.g. aneurysm)

## Treatment

- **Non-secretory pituitary microadenomas** (incidentalomas) >> no treatment (only follow-up with serial MRI)
- **Prolactinomas** (PRL is usually >6000mU/ml)
  - First-line: dopamine agonists (e.g., cabergoline, bromocriptine) >> shrink pituitary adenoma.
  - Second-line: trans-sphenoidal hypophysectomy ± adjuvant radiotherapy
- **Other pituitary adenomas**
  - First-line: transsphenoidal hypophysectomy
  - Second-line: Medications ± pituitary irradiation

# Growth hormone (GH)

It is an **anabolic** hormone secreted by the **somatotroph** cells of the **anterior** lobe of the pituitary gland.

It has actions on **multiple** organ systems and is important in postnatal growth and development.

GH is also responsible for changes in protein, lipid, and carbohydrate **metabolism.**

**Which signaling pathways does growth hormone (GH) use?**
**Atyrosine kinase receptor**

## Mechanism of action:

- Acts on a **transmembrane receptor** for growth
- Binding of GH to the receptor leads to receptor dimerization.
- Acts **directly** on tissues (e.g. stimulates division and multiplication of cartilage chondrocytes or bone osteoblasts) and **indirectly** via insulin like growth factor 1(IGF-1), primarily secreted by the liver.

### Conditions associated with GH disorders:

- Excess GH: acromegaly
- GH deficiency: resulting in short stature

**GH along with cortisol and adrenalin (called counter-regulatory hormones) tell the body to increase the availability of glucose – so it counters the effect of insulin.**

### Conditions associated with GH disorders

- GH deficiency: resulting in short stature
- excess GH: acromegaly

The commonest side effect of recombinant human GH therapy is **fluid retention** so **may be associated** with **IIH (Idiopathic intracranial hypertension)**, though other side effects include: gynaecomastia, hypertension, and atrial fibrillation.

**IGF-1** are often **increased** in **Acromegaly** and **pregnancy.**
**Reduced** IGF-1 is typically found in:

- **Adult GHD**
- **Liver cirrhosis** due to reduced synthesis
- **CKD**
- **DM**, and
- **Starvation.**

# Growth hormone deficiency (GHD)

## Causes

- Pituitary tumours or their treatment, (e.g. surgery, cranial irradiation) is the most common cause.
- Any other cause of hypopituitarism (see hypopituitarism topic)

## Features

- **In infancy** are hypoglycemia and micropenis is the primary manifestations
- **In early childhood:** growth failure is the primary manifestation. causes premature fusion of the epiphyseal portion of the bone.
- **In adults**
  - ↑↑ fat mass
  - ↓↓ lean body mass
  - ↓↓ bone mineral density (BMD) >> osteopenia/osteoporosis
  - ↓↓ energy, ↓↓quality of life (QoL)
  - ↓↓ sweating >> Dry skin
  - ↑↑ greater mortality, ↑↑ cardiovascular risk
  - ↑↑ insulin resistance
  - Dyslipidaemia (↑LDL).

## Diagnosis

Decreased serum insulin-like growth factor-1 (IGF-1) levels: **may be normal in up to 50%.**

Dynamic tests of GH secretion

- **Insulin tolerance test (ITT): the gold standard for the diagnosis**
  - **insulin-induced hypoglycaemia >> GH response of less than 9 mU/L (3 ng/ml) >> GHD**
  - Causes of false positive test: Obesity >> ↓ GH response to insulin-> false positive test
  - Contra-indications to ITT:
    - **seizures (eg: in epilepsy)**
    - **IHD,** Abnormal ECG
    - basal cortisol levels <100 nmol/L Glycogen storage disease
    - **Elderly** (due to high risk of hypoglycaemia)
- Alternative test if ITT is contraindicated:
  - **arginine-GHRH stimulation test**
  - **glucagon-GH-releasing hormone stimulation test**

Two tests of GH stimulation test are required before making the diagnosis.

## Treatment

Subcutaneous injections of recombinant human growth hormone.

- **Criteria for GH treatment:** only if **all the following three criteria are met**
  - Severe GH deficiency, defined as a peak GH response of less than 9 mU/litre (3 ng/ml) during an **insulin tolerance test.**
  - Impairment of **QJality** of Life (**QoL**): 'Quality of life assessment of growth hormone deficiency in adults' (QoL-AGHDA) score ≥ 11.
  - Treatment for other pituitary hormone deficiencies

## Adverse effects of GH replacement

- Sodium and water retention
  - Weight gain
  - Carpal tunnel syndrome
- Hyperinsulinaemia
- Arthralgia (possibly due to intra-articular cartilage swelling)
- Myalgia
- **Benign intracranial hypertension** (resolves on stopping treatment)

## Contraindications to GH replacement

- Active malignancy
- Benign intracranial hypertension
- Pre-proliferative/proliferative retinopathy in diabetes mellitus

**Which treatment is most appropriate for patients with preserved pituitary function and deficiencies in growth hormone (GH) and adrenocorticotrophic hormone (ACTH)?**

- **Cortisol replacement therapy only.**
  - **GH deficiency can be caused by hypoadrenalism. Concomitant cortisol and GH replacement therapies are not appropriate because cortisol alone may be sufficient to restore GH secretion.**

**MRCP-UK. SCE. Sample question**

patients with childhood-onset GHD who are candidates for GH therapy after adult height achievement. What is the most appropriate next step in management?

>> should be **retested for GHD**

# Acromegaly

In acromegaly there is excess growth hormone secondary to a **pituitary adenoma** in **over 95% of cases.**
A minority of cases are caused by ectopic GHRH or GH production by tumors e.g., pancreatic.
A significant percentage of GH secreting tumors are thought to have a **mutation** in the **alpha** sub-unit of the stimulatory guanosine triphosphate (**GTP**) binding protein >>> this leads to persistent **elevation of cyclic adenosine monophosphate (↑cAMP)** and hence production of excess growth hormone.

## Features:

- Coarse facial appearance, spade-like hands, increase in shoe size.
- Large tongue, prognathism, interdental spaces.
- **Excessive sweating** and oily skin (The increased sweating is caused by **sweat gland hypertrophy).**
- Features of pituitary tumour: hypopituitarism, headaches, **bitemporal hemianopia.**
- **Raised prolactin in 1/3 of cases → galactorrhoea.**
- 6% of patients have **MEN-1**.
- **Pseudogout** is seen in acromegaly but not gout.
- Goiter is seen in 20%, along with other soft tissue swelling.
- Phosphate is elevated but calcium is not significantly increased.

A 60-year-old man with acromegaly. Note the coarse facial features and moderate prognathism

Patient with acromegaly producing hands that are large and doughy with widened fingers.

## Complications:

- **Hypertension.**
- **Diabetes (>10%).**
- **Cardiomyopathy.**
- Colorectal cancer.
- Insulin resistance and impaired glucose tolerance (40%)/diabetes mellitus (20%).
- Obstructive sleep apnoea: due to soft tissue swelling in nasopharyngeal region.
- Osteoarthritis, Arthralgia, **Pseudogout**
- Carpal tunnel syndrome: Positive Tinel's sign
- 6% of patients have MEN-1, hypercalcemia >> primary hyperparathyroidism >> MEN 1.

**N.B:** Acromegaly is associated with systemic HTN rather than pulmonary HTN

## Investigations:

- **Growth hormone (GH) levels vary during the day and its release is pulsatile and so therefore not diagnostic.**
- **Serum IGF-1 levels** have now overtaken the oral glucose tolerance test (OGTT) with serial GH measurements as the first-line test. The OGTT test is recommended to **confirm the diagnosis** if IGF-1 levels are raised.
- **The Endocrine Society guidelines gives the following statement:**
  - **We recommend measurement of IGF-1 levels in patients with typical clinical manifestations of acromegaly, especially those with acral and facial**
  - **Pituitary MRI: usually demonstrates the tumour (98%) If no pituitary tumor detected >> serum GHRH + radiology of the chest and abdomen to detect ectopic GHRH-secreting tumor (usually a GHRH-secreting carcinoid of lung or pancreas.)**

In active acromegaly with associated diabetes mellitus >> There is insulin resistance

Acromegaly >> risk of colon cancer >> regular colonoscopy screening, starting at the age of 40 years.

### Oral glucose tolerance test

- in normal patients GH is suppressed to < 2 mu/L with hyperglycaemia
- in acromegaly there is no suppression of GH
- may also demonstrate impaired glucose tolerance which is associated with acromegaly

## Management

**1) Trans-sphenoidal surgery (TSS)** is **first-line treatment for acromegaly** in the **majority** of patients.

**If a pituitary tumor is inoperable or surgery unsuccessful then medication may be indicated:**

**2) Dopamine agonists:**

- For example, **Bromocriptine.**
- The first effective medical treatment for acromegaly, however now superseded by somatostatin analogues.
- Effective only in a minority of patients
- It is only more useful for treatment pf prolactinomas rather than GH producing tumors.

**3) Somatostatin analogue:**

- For example, **Octreotide.**
- Effective in 50-70% of patients.
- It is the **initial first medical therapy of choice.**
- May be used as an adjunct to surgery.
- It is useful in controlling cardio-metabolic risk factors prior to surgery.
- It is associated with **tumour shrinkage** and resolution of some clinical symptoms prior to progression to trans-sphenoidal surgery.

**4) Pegvisomant:**

- It is genetically modified analogue of human GH and is a **highly selective GH receptor antagonist >>** prevents dimerization of the GH receptor.
- **Once daily S/C** administration.
- Very effective as It has been shown to normalize insulin-like growth factor-I (IGF-I) levels in 90-100% of patients with a history of acromegaly.
- It is the usual **second** line of **medical** therapy.
- GH levels increase during treatment and **no decrease in tumor size** is seen, as such the major use of pegvisomant is in patients who have an **inadequate** response to surgery or radiotherapy.
- **Doesn't reduce tumour volume** therefore **surgery** still needed **if mass effect.**

**External irradiation** is sometimes used for older patients or following failed surgical/medical treatment.

If patient does **not wish** for **surgery** at present but agree to try **medical** therapy >>>> **1) Octreotide**, then **2) Pegvisomant.**

## Summary of types of diabetes:

| Type | Notes |
|---|---|
| **Type 1 diabetes mellitus (T1DM)** | Autoimmune disorder where the insulin-producing beta cells of the islets of Langerhans in the pancreas are destroyed by the immune system<br>This results in an absolute deficiency of insulin resulting in raised glucose levels<br>Patients tend to develop T1DM in childhood/early adult life and typically present unwell, possibly in diabetic ketoacidosis |
| **Type 2 diabetes mellitus (T2DM)** | This is the most common cause of diabetes in the developed world. It is caused by a relative deficiency of insulin due to an excess of adipose tissue. In simple terms there isn't enough insulin to 'go around' all the excess fatty tissue, leading to blood glucose creeping up. |
| **Prediabetes** | This term is used for patients who don't yet meet the criteria for a formal diagnosis of T2DM to be made but are likely to develop the condition over the next few years. They, therefore, require closer monitoring and lifestyle interventions such as weight loss |
| **Gestational diabetes** | Some pregnant develop raised glucose levels during pregnancy. This is important to detect as untreated it may lead to adverse outcomes for the mother and baby |
| **Maturity onset diabetes of the young (MODY)** | A group of inherited genetic disorders affecting the production of insulin. Results in younger patients developing symptoms similar to those with T2DM, i.e. asymptomatic hyperglycaemia with progression to more severe complications such as diabetic ketoacidosis |
| **Latent autoimmune diabetes of adults (LADA)** | The majority of patients with autoimmune-related diabetes present younger in life. There are however a small group of patients who develop such problems later in life. These patients are often misdiagnosed as having T2DM |
| **Other types** | Any pathological process which damages the insulin-producing cells of the pancreas may cause diabetes to develop. Examples include chronic pancreatitis and haemochromatosis.<br>Drugs may also cause raised glucose levels. A common example is glucocorticoids which commonly result in raised blood glucose levels |

- Antihypertensive: **CCB (verapamil), methyldopa**
- Psychotropic agents: **SSRI, TCA**
- Antipsychotics: **Risperidone**
- Neuroleptics: **phenothiazines, haloperidol, sulpiride (Dogmatil®)**
- **Opiates** and opiate antagonists
- **Protease inhibitors**
- **Combined oral contraceptive pills**

3) **Neurogenic:** via autonomic nervous system.
   - Chest wall injury
   - Breast stimulation
   - Breast feeding
4) **Physiological** causes: via oestrogen stimulation.
   - **Pregnancy**, coitus
   - Exercise, sleep, stress
5) **Increased prolactin production:**
   - Ovarian: **polycystic ovarian syndrome**
   - Pituitary tumours: adenomas (**prolactinoma**), hypothalamic **stalk** compression, hypophysitis
6) **Reduced prolactin elimination:**
   - Renal failure
   - Hepatic insufficiency

The **first test** to do when seeing a lady with **hyperprolactinaemia** is to exclude **pregnancy**, as it is the **most common cause**.

**Hypothyroidism** is not an uncommon cause of hyperprolactinaemia and should be **part of the work up of all patients with an elevated prolactin and secondary amenorrhoea.**

**Significant hypothyroidism (TSH >10)** can result in raised levels of **TRH** (thyrotropin-releasing factor). This can act as prolactin-releasing factor and bind to the receptors, resulting in the release of prolactin. **TTT: Thyroxin.**

**Prolactin levels less than 1000** are most likely to be **drug related**.
**Microprolactinoma** is associated with levels of prolactin of **1,000-3,000** mU/L.
In **Macroprolactinomas**, the prolactin concentration is **more than 3000 mU/L (with levels of prolactin of 3,000-6,000 or higher) (more than 6000 is suggestive of macroprolactinoma)**.
**MRI Pituitary: hypo**-intense lesion on **T1** weighted scanning.

**EX:** The 1500 mU/L is an option of an intermediate level between that seen with drug related hyperprolactinaemia and a microprolactinoma.

**Hyperprolactinaemia is typical of pregnancy.**
Microprolactinomas rarely expand during pregnancy (less than 1%) and the prolactin concentration is no guide to this and does not need to be measured.

Features that would give rise to suspicion of expansion would include field constriction and atypical headache symptoms. Severe frontal headache may suggest apoplexy for instance.

Headaches are common in pregnancy.

A Non-functioning pituitary tumour (**NFPT**) may cause **hyperprolactinaemia but of less than 2000 mU/L** through **local stalk compression** and may be associated with **low Estradiol, FSH, LH** and **high TSH** (dt it may occasionally secrete small amounts of TSH).
**MRI** brain is needed.
**Surgery** is the mainstay of therapy for **NFPT** as the tumour is highly **unlikely** to respond significantly to dopamine agonists or somatostatin.
After surgery patient should receive **replacement therapy** with **hydrocortisone** 10 mg am, 5 mg pm, **thyroxine** 150 µg daily (with follow up by free T4 not TSH) , **testosterone** 250 mg IM monthly and **growth hormone**.
**EX**: A 30-year-old female presents with galactorrhoea and an **elevated prolactin** of 1200 mU/L (50-450) and **low oestradiol** concentration of 100 pmol/L (130-450), **low FSH and LH** with raised TSH. Which of the following is the likely cause >>> **NFPT**.

**N.B:** Prolactinoma management >>> **Medical ttt** is almost always **first line even if visual field defects are present**.

**The dopamine agonists**, **Bromocriptine**, and **Cabergoline** (activate D2 receptors) reduce prolactin levels thereby allowing oestrogen levels to normalise. They are effective in most patients, but do normally need to continue long-term.

**Cabergoline** is an ergot-derived dopamine agonist, dose once or twice / week.

**Ropinirole** is non-ergot-derived dopamine agonists

**SE** of dopamine agonists: **Pericarditis, pericardial effusion, cardiac valve regurgitation and pulmonary hypertension.**

**Contraindications** to treatment are cardiac valve fibrosis and pulmonary fibrosis.

**EX:** Male pt. with erectile dysfunction, loss of libido and microprolactinaemia >>> start Cabergoline >>> Chest pain pericarditis >>> **Ropinirole** will be an appropriate alternative in this case.

Pituitary surgery is rarely required in prolactinomas and is generally reserved for patients intolerant of or resistant to dopamine agonist therapy.

The main indication for surgery are tumours resistant to dopamine agonists.

Outcomes for **surgery** are generally **poor** with high risk of **recurrence** ⊗

Many women with a microprolactinoma can be maintained on dopamine agonists without the need to progress to surgery which itself carries associated morbidity.

As such there is no need to stop therapy or progress to surgery before trying for a child, indeed stopping therapy will reduce the chance of ovulation.

**Combined oral contraceptives can lead to mild rises in serum prolactin**, and therefore should only be used with caution in patients with prolactinomas.

There is no evidence that bromocriptine is teratogenic from available data on use in pregnancy. There are less data on cabergoline and so this is not recommended.

**Once pregnancy is established, bromocriptine** is not necessarily required, and so most physicians recommend **stopping** it for the duration.

There is no evidence that bromocriptine is required to be continued throughout the pregnancy.

**EX**: Female patient with inability to achieve pregnancy with pituitary microadenoma on bromocriptine and want to get pregnant >>> She should know that **within a few months** menstrual cycles are likely to return and that pregnancy has a much higher probability and so she should **stop** her **bromocriptine once** she knows she is pregnant (i.e. **as soon as** she has a positive pregnancy test) (**NOT** prior to trying to get pregnant).

**EX**: Any patient has a **co-incidentally noted pituitary tumour** and has **no** endocrine symptoms (i.e. **NORMAL OF ALL**: normal visual field, normal thyroid, normal synacten test, normal testosterone/oestrogen, FSH, LH) >>> so **reassurance, observation and repeat scanning.**

## Craniopharyngioma

It is a **slow-growing, calcified cystic tumour** arising from the remnants of the craniopharyngeal duct.

It compromises about 4.5% of all childhood tumours.

It is slightly more common in **males** than females.

The symptoms develop very slowly and usually become manifest once the tumour has attained a diameter of 3 cm.

The commonest presentation in young patients is **growth failure** and **delayed puberty**.

**CT brain: suprasellar calcified cyst** with the cyst content having the same density as the CSF (the calcification is more common in children than in adults).

**Treatment: Surgery** ± postoperative radiotherapy.

**EX: Male boy 14** years old with **short stature, delayed puberty**, with 6 months **headache, CT brain: suprasellar calcified cyst >>> Craniopharyngioma.**

## Antidiuretic hormone (ADH)

- ADH is a (9) **nona-peptide manufactured (synthesised)** in the **supra-optic (SO)** and **paraventricular (PV) nuclei** of the **hypothalamus** and **released (secreted)** from the **posterior** pituitary.
- It **acts on** the **collecting ducts** improving water permeability and hence water retention.
- ADH binds to **V2 receptors** which are found on the peritubular surface of cells in the **distal convoluted tubule** and **medullary collecting duct.**
- This leads to **insertion of aquaporin-2 channels** into the luminal membrane, enhancing permeability to water.
- It promotes water reabsorption in the collecting ducts of the kidneys by the insertion of aquaporin-2 channels.
- There are multiple subtypes of aquaporin channels, some of which, such as aquaporin 3, are involved in passage of water through the skin.

- **V1 receptors** are involved in mediating **platelet aggregation** and do not have a role in controlling water reabsorption.

Antidiuretic hormone (ADH) >>> site of action >>> collecting ducts

- ADH is known to **increase platelet aggregation**, as such it may be considered **prothrombotic** at **high** dose.
- ADH actually leads to **increased** factor **VIII 8** production, and as such may be of utility in **treating some patients with haemophilia A.**
- ADH leads to uterine and GI **smooth muscle contraction** and indirectly leads to a reduction in coronary artery blood flow.
- Carbamazepine as well as other agents such as thiazides and SSRIs may potentiate its release.
- Ethanol usually inhibits release.

**MRCPI part 1 exam: H/O RTA + rapid pulse and low BP + low Na.**
**What is the most likely explanation for this patient's hyponatremia?**

- **Physiologic ADH (vasopressin) secretion**
  - **Hyponatremia that develops after massive hemorrhage is likely dilutional.**
  - When baroreceptors detect decreases in effective arterial volume, such as after massive blood loss, they cause antidiuretic hormone (ADH) to be released from the pituitary gland to increase renal reabsorption of free water, diluting serum sodium levels and causing hyponatremia.

**What is the appropriate management of this patient?**

- **normal saline.**
  - Management of **hypovolemic hyponatremia** includes volume repletion with normal saline.
  - Correction of hypovolemia removes the stimulus to release ADH, causing free water excretion by the kidneys, which leads to rapid correction of serum sodium levels.
  - volume repletion with normal saline must occur at a slow rate, because rapid correction of hyponatremia can cause central pontine myelinolysis.

**exam part 1:** Which adaptive mechanism that prevent dying from dehydration?
**>> Increase of aquaporin-2 in the collecting duct.**
ADH (vasopressin) >> ↑ **aquaporin-2** expression >> ↓ water excretion >> protect against dehydration

**MRCPUK part 1 exam:** You are reviewing a patient with a history of cranial diabetes insipidus. He is passing 4–6 litres of urine per day.
Expression of which channel is likely to be decreased most in the collecting duct?
**>> Aquaporin 2**

- It is found in the apical membranes of collecting duct principal cells.
- Aquaporin 2 gene expression is increased by vasopressin, which leads to increased re-absorption of free water. Expression is therefore downregulated in response to cranial diabetes insipidus.

# SIADH (↑ADH)

**Essential criteria:** In this condition, ADH is secreted in the absence of an appropriate physiological stimuli such as decreased effective circulatory volumeor hyperosmolarity.
SIADH is a diagnosis of exclusion:

## Diagnostic criteria:

| Diagnostic criteria for SIADH | |
|---|---|
| | Clinical and/or laboratory findings |
| **Hyponatremia** | Serum sodium < 135 mEq/L |
| **Hypoosmolality** | Serum osmolality < 275 mOsm/kg |
| **Concentrated urine** | Urine osmolality > 100 mOsm/kg |
| **Elevated urinary sodium** | Urine sodium concentration > 20 mEq/L |
| **Euvolemia** | • No signs of hypovolemia<br>• No signs of hypervolemia (e.g. oedema) |
| **No alternative causes** | • Normal thyroid, adrenal, and renal function >> Other causes of euvolemic hypotonic hyponatremia have been excluded (e.g., hypothyroidism, hypercortisolism, AKI)<br>• It is important to note that normal thyroid is referring to primary hypothyroidism. **Euthyroid sick syndrome does not preclude the diagnosis of SIADH.** |

**N.B: Other points to diagnose SIADH:**

- Maintained hypervolemia.
- Suppression of RAS (renin angiotensin system)
- No equal concentration of ANP (atrial natriuretic peptide)
- Normal serum creatinine.
- Normal acid base and K balance.
- ↓ BUN
- ↓ Uric acid
- ↓ Albumin

**Also there is:**

- Failure to correct hyponatraemia after 0.9% saline infusion.
- fractional sodium excretion >0.5%.
- Fractional urea excretion >55%.
- Fractional uric acid excretion >12%.
- Correction of hyponatraemia through fluid restriction.

**Thyroid function test** should be checked in an elderly patient presenting with unexplained personality change or cognitive impairment and need to be normal in order to make the diagnosis of SIADH.

## Causes of SIADH:

| Category | Examples |
|---|---|
| **Malignancy** | • **Small cell lung cancer (SCLC)**<br>• also: pancreas, prostate |
| **Neurological** | • Stroke<br>• Subarachnoid haemorrhage<br>• Subdural haemorrhage<br>• Meningitis/encephalitis/abscess<br>• Head injury and neurosurgery operation |
| **Infections** | • Tuberculosis<br>• Pneumonia |
| **Drugs** | • **Sulfonylureas**<br>• **SSRIs**<br>• **TCA**<br>• **Antipsychotics:** (Haloperidol, quetiapine, clozapine)<br>• **Carbamazepine**<br>• **Thiazide**<br>• Vincristine<br>• Cyclophosphamide<br>• **Omeprazole** |
| **Other causes** | • Positive end-expiratory pressure (PEEP)<br>• **Porphyrias** |

## Differential diagnosis

### Cerebral salt wasting (CSW)

- **hypovolaemia**, hyponatraemia and grossly elevated urine sodium (**>100**), with polyurea in patient with head injury.
- it **treated with replacing fluid and sodium losses**, whereas SIADH treated with fluid restriction

## Management

- Treating the underlying **cause**.
- Correction must be done **slowly** to **avoid** precipitating **central pontine myelinolysis (CPM).**
- **Fluid restriction** to less than 1 litre per day.
- **ADH (vasopressin) V2 receptor antagonists** (Tolvaptan) have been developed.

- **Demeclocycline**: reduces the responsiveness of the collecting tubule cells to ADH >> it will induce nephrogenic **D.I.**: reserved for more refractory cases.
- **Hypertonic saline** in very severe cases e.g. fits.

## Diabetes insipidus (DI) (= NO ADH)

DI is a condition characterised by either a deficiency of antidiuretic hormone, ADH, (cranial DI) or an insensitivity to antidiuretic hormone (Nephrogenic DI).

This can be **confirmed** with a **water deprivation test** where failure of urine concentration would be expected.

### Causes of cranial DI:

- **Idiopathic**
- **Post head injury**
- Pituitary surgery as in TSS (Tran sphenoidal surgery).
- Craniopharyngiomas.
- Granulomatous disease such as **Histiocytosis X, Tuberculosis**, and **Sarcoidosis** could infiltrate hypothalamus or pituitary gland.
- **DIDMOAD** is the association of cranial Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy and Deafness (also known as **Wolfram's syndrome).**

### Causes of nephrogenic DI (NDI):

- **Genetic:**
  - The **more** common form affects the vasopressin (ADH) receptor **(V2 ADH receptor gene mutation)**
  - The **less** common form results from a **mutation** in the **gene** that **encodes** the **aquaporin 2 channel.**
  - Nephrogenic DI is usually **X linked recessive.**
- **Electrolytes:**
  - **hypercalcaemia,**
  - **hypokalaemia.**
- **Drugs: Lithium** and **Demeclocycline (e.g. Doxycycline)**
- **Tubulo-interstitial disease: post-obstructive uropathy, pyelonephritis, sickle-cell nephropathy, amyloidosis.**

### Features:

- **Polyuria**
  - urine output is > 50 ml/kg per day (3000 ml for a 60-kg female).
  - Nocturia → Restless sleep, daytime sleepiness **(In the absence of nocturia, diabetes insipidus is very unlikely)**

- **Polydipsia**

**DD: Polyuria:**
1) DM
2) DI
3) Psychogenic polydipsia
4) Drug abuse (thiazide diuretic)

## Diagnosis

- **High plasma osmolarity (↑ Serum Na),**
  - **plasma osmolality >305 mOsmol/kg**
  - serum [Na] >145 mmol/L,
- **Low urine osmolarity**
  - **urine osmolality <200 mOsm/kg**
  - urinary [Na] 20-60 mmol/L
  - urinary specific gravity <1.005.
- **Water deprivation test**
- CT scan or MRI of the head should be conducted to rule out brain tumors

Measuring **plasma and urine osmolality** is the **first** step in diagnosis of DI, when **inappropriately low urine osmolality** in the presence of a raised or normal (not low) plasma osmolality, this is suggestive of diagnosis of DI and **the water deprivation test** would be the obvious **next** step.

**Normal plasma osmolality = 270-300 mOsm/kg**
**Normal urinary osmolality = 350-1000 mOsm/kg**

## Management

**Central (DI)**

- Mild CDI (urine output 3-4 litres/24 hours) >>> increase oral water intake.
  - oral or nasogastric water is the replacement fluid of choice as this route provides a good buffer against rapid changes in serum sodium.
- If the urine output continues to be greater than 250 ml/hr >>> **Desmopressin** (Synthetic ADH) **is the drug of choice.**

**Nephrogenic (DI)** >> correct the underlying cause (e.g. stop the responsible drug)

- Thiazide diuretic (eg, hydrochlorothiazide), **amiloride** (K- sparing diuretic) >>> act on Distal Convoluted Tubule and inhibit the NaCl cotransporter and thus exaggerate the hypovolemia and increase an already activated renin – angiotensin - aldosterone system (RAAS)

further. This mechanism stimulates proximal tubule sodium and water reabsorption resulting in less volume delivery to the collecting tubules where ADH work.

- NSAIDs (indomethacin) >>> inhibit prostaglandin synthesis, which has antagonistic effects on ADH.
- Amiloride is the drug of choice for lithium - induced nephrogenic DI >>> **blocks the epithelial sodium channel (ENac) in the collecting duct where lithium enter and causes DI.**

**Rate of hypernatraemia correction**

- Symptomatic patients with acute hypernatraemia {developed within 48h) >> 5mmol/L in the first hour (or until symptoms improve) and is limited to 10mmol/L per 24h.
- No or mild symptoms >> the rate of correction should not exceeding 0.5mmol/L/h and is limited to 10mmol/L/24h.

**Fluid status in DI**

- Total body water: decrease,
- Extracellular fluid: increase,
- Intracellular fluid: decrease

**DI >> losing hypotonic fluid in the urine >> ↑ osmolarity of the extracellular fluid >> water will flow out of the intracellular compartment and into the extracellular compartment >> ↑extracellular fluid volume and ↓intracellular fluid volume.**

**MRCP UK part 1 exam:** A mutation in the gene that encodes aquaporin 2 is most likely to result i? **>> Diabetes insipidus**

Which part of the nephron is most affected in diabetes insipidus?
**>> Cortical and medullary collecting tubules**

## Water deprivation test

**Method:**

- Prevent patient drinking water for **8 hours** or until 5% of body weight is lost.
- Ask patient to empty bladder.
- Hourly body weight.
- Plasma osmolality is measured every 4 hours.
- Urine osmolality and volume are measured every 2 hours.
- **Demopressin (DDAVP) 2mcg IM/SC** is given with urine volume & urine and serum osmolality are measured over the next 4 hours.

| time | Weight (kg) | Plasma osm | Urine osm | Urine vol (ml) |
|---|---|---|---|---|
| 8 am | 66.5 | 285 | - | - |
| 9 am | - | - | 110 | 200 |
| 10 am | - | - | 200 | 290 |
| 11 am | - | - | 240 | 220 |
| 12 midday | 66 | 300 | 290 | 200 |
| 1 pm | - | - | 310 | 200 |
| 2 pm | - | - | 320 | 202 |
| 3 pm | - | - | - | 150 |
| 4 pm | 65.2 | 304 | 340 | 156 |
| DDAVP 1 microgram SC given at 4 pm and permitted to drink | | | | |
| 6 pm | 66.4 | 290 | 810 | 15 |

**Cranial DI post pituitary surgery** is very common, the most appropriate initial therapy is **match fluid output with appropriate adequate fluid replacement**, only some patients will require long term DDAVP replacement.

**EX:** Female patient with depression on lithium, she has dehydration, drowsiness, confusion, polyuria and increasing thirst, ↑ Serum Na 155 >>> **Nephrogenic DI.**

**EX:** A 24-year-old **female** presents with a 2 week history of **polyuria** and **polydipsia** together with frequent nocturia + **low Na** + **low K** + **High Ca** + **High glucose** + **High serum osmolality** >>> **Drug abuse (Thiazide)**

**EX:** Case of cranial DI
- If serum osmolality rise above 305 mOsmol/kg, then the patient is said to have **DI** and the test is stopped.
- If urine osmolality < 300 mOsmol/kg after fluid deprivation, rising to above 800 mOsmol/kg or more than 50% after desmopressin injection >>>**Cranial DI.**
- If urine osmolality < 300 mOsmol/kg after fluid deprivation, remaining at less than 300 mOsmol/kg or only slight increase in urine osmolality < 50% after desmopressin >>> **Nephrogenic DI.**
- If urine osmolality reaches level > 800 mOsmol/kg **without** desmopressin >>> **primary polydipsia.**
- If urine osmolality is intermediate 300-800 mOsmol/kg, and fails to rise above 800 after desmopressin >>> **partial** DI or polydipsia.

| | | Starting plasma osm. | Starting urine osm. | Urine osm. post-DDAVP |
|---|---|---|---|---|
| 1 | **Normal** | Normal (275- 300) | > 600 | > 600 |
| 2 | **Psychogenic polydipsia** | **Low** | > 400 | > 400 |
| 3 | **Cranial DI** | **High** | < 300 | > 600 |
| 4 | **Nephrogenic DI** | **High** | < 300 | < 300 |
| 5 | **SIADH** | **Low** | High | — |

A dramatic improvement in the ability of the kidneys to concentrate urine following the administration of DDAVP points towards a diagnosis of cranial diabetes insipidus

## Differentiate psychogenic polydipsia from CDI and NDI:

- Patients with this disorder ingest and excrete up to 6L of fluid/day and are often emotionally disturbed.
- **Unlike patients with CDI and NDI, they do not have nocturia, nor does increased thirst wake them at night.**
- Patients with acute psychogenic polydipsia can concentrate their urine during a water deprivation test but chronic water intake diminishes medullary tonicity in the kidney.
- Patients with **long-standing polydipsia** are not able to concentrate their urine to maximal levels during water deprivation, a response similar to that of patients with partial central diabetes insipidus.
- However, **unlike central diabetes insipidus, patients of psychogenic polydipsia show no response to exogenous ADH after water deprivation**. This response resembles nephrogenic diabetes insipidus, but **ADH levels** are low in psychogenic polydipsia and high in nephrogenic polydipsia.

# Pituitary apoplexy

**Sudden** enlargement of pituitary tumour **secondary** to haemorrhage or infarction. A pituitary adenoma usually pre-exists.
Endocrinologically, the main initial problem is a **lack of adrenocorticotropic hormone (ACTH),** which results in a lack of cortisol and the features of an **'Addisonian crisis'**, i.e. hypotension, hyponatraemia, hyperkalaemia and hypoglycaemia. Subacutely, there can be deficiency in thyroid stimulating hormone (TSH) and gonadotropins (LH and FSH).
The mild hyponatraemia may be a consequence of the either SIADH or secondary hypoadrenalism.

## Features:

### Features of raised intracranial pressure (↑↑ ICP)

- **Sudden onset headache similar to that seen in SAH.**
- **Vomiting**
- **Neck stiffness**
- **Visual field defects:** classically **bitemporal** superior quadrantic defect.
- **Extra ocular** nerve palsies in up to **80%**, with **III** nerve palsy the commonest finding.
- Features of pituitary insufficiency e.g. **Hypotension** secondary to **hypoadrenalism.**

The combination of **headache**, vomiting, **visual disturbance** and **hormonal** dysfunction should lead you to consider a diagnosis of pituitary apoplexy.

**MRT pituitary** to confirm the diagnosis

**Treatment:** **Hydrocortisone IV** should be given to prevent addisonian crisis.

- Over the long-term > > corticosteroid, testosterone and thyroid hormone replacement.

**EX:** A 47-year-old man presents to the Emergency Department with a **3 day history of severe headache** associated with **vomiting**. There is no past medical history of note. On examination **BP is 98/62 mmHg**, pulse is 108 bpm and temperature is 37.0°C. There is **mild neck stiffness** and a **partial third nerve palsy of the left eye**. Blood rests reveal: **$Na^+$ = 130, K= 5.2, Low free T4.** The most likely diagnosis is >>> **Pituitary apoplexy**.

# Thyroid gland disorders

## introduction

Disorders of thyroid function are very commonly encountered in clinical practice. Around 2% of the UK population has hypothyroidism (an under active thyroid gland) whilst around 1% have thyrotoxicosis (an over active gland). Both hypothyroidism and hyperthyrodism (also known as thyrotoxicosis) are around 10 times more common in women than men.

### How are thyroid problems classified?

Hypothyroidism may be classified as follows:

- primary hypothyroidism: there is a problem with the thyroid gland itself, for example an autoimmune disorder affecting thyroid tissue (see below)
- secondary hypothyroidism: usually due to a disorder with the pituitary gland (e.g.pituitary apoplexy) or a lesion compressing the pituitary gland
- congenital hypothyroidism: due to a problem with thyroid dysgenesis or thyroid dyshormonogenesis

**Whilst there are a number of causes thyrotoxicosis the vast majority are primary in nature. Congenital thyrotoxicosis is not seen and secondary hyperthyroidism is rare, account for less than 1% of cases.**

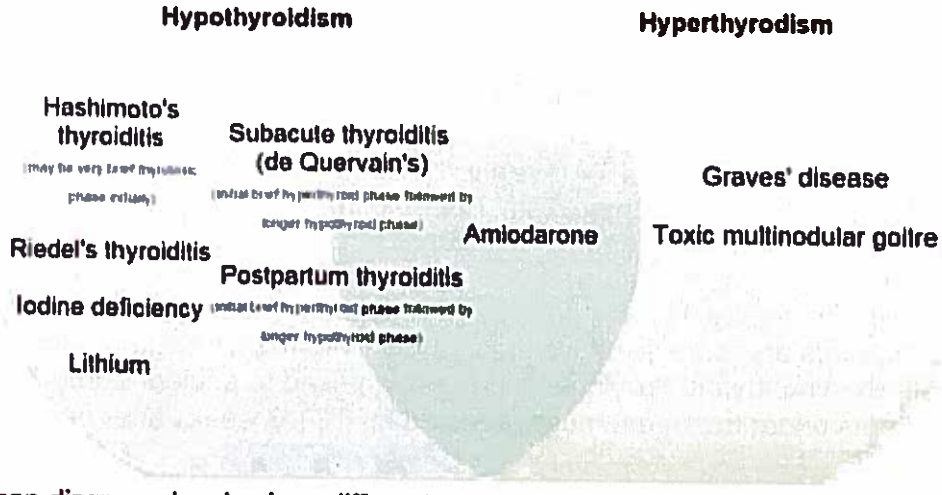
### What causes thyroid problems?

- The majority of thyroid problems seen in the developed world are a consequence of autoimmunity.

**The table below shows the different autoimmune problems which cause thyroid dysfunction:**

| | Hypothyroidism | Thyrotoxicosis |
|---|---|---|
| **Most common cause** | **Hashimoto's thyroiditis**<br>• most common cause in the developed world<br>• autoimmune disease, associated with type 1 diabetes mellitus, Addison's or pernicious anaemia<br>• may cause transient thyrotoxicosis in the acute phase<br>• 5-10 times more common in women | **Graves' disease**<br>• most common cause of thyrotoxicosis<br>• as well as typically features of thyrotoxicosis other features may be seen including thyroid eye disease |
| **Other causes** | **Subacute thyroiditis (de Quervain's)**<br>• associated with a painful goitre and raised ESR<br>**Riedel thyroiditis**<br>• fibrous tissue replacing the normal thyroid parenchyma<br>• causes a painless goitre<br>**Postpartum thyroiditis**<br>**Drugs**<br>• lithium<br>• amiodarone<br>**Iodine deficiency**<br>• the most common cause of hypothyroidism in the developing world | **Toxic multinodular goitre**<br>• autonomously functioning thyroid nodules that secrete excess thyroid hormones<br>**Drugs**<br>• amiodarone |

It should be remembered that a lot of the conditions mentioned above don't always cause either hypothyroidism or hyperthyroidism, there is sometimes some overlap, as shown below:




Venn diagram showing how different causes of thyroid dysfunction may manifest. Note how many causes of hypothyroidism may have an initial thyrotoxic phase.

## Symptoms and signs

Thyroid disorders can present in a large variety of ways. Often (but not always) the symptoms present are the opposite depending on whether the thyroid gland is under or over active, for example hypothyroidism may result in weight gain whilst thyrotoxicosis normally leads to weight loss

| Feature | Hypothyroidism | Thyrotoxicosis |
|---|---|---|
| General | Weight gain<br>**Lethargy**<br>cold intolerance | Weight loss<br>'Manic', restlessness<br>Heat intolerance |
| Cardiac | -effusion ,bradycardias | **Palpitations**, may even provoke arrhythmias e.g. atrial fibrillation |
| Skin | Dry (anhydrosis), cold, yellowish skin<br>Non-pitting oedema (e.g. hands, face)<br>Dry, coarse scalp hair, loss of lateral aspect of eyebrows | Increased sweating<br>Pretibial myxoedema: erythematous, oedematous lesions above the lateral malleoli<br>Thyroid acropachy: clubbing |
| Gastrointestinal | Constipation | Diarrhoea |
| Gynaecological | Menorrhagia | Oligomenorrhea |
| Neurological | Decreased deep tendon reflexes<br>Carpal tunnel syndrome | **Anxiety**<br>**Tremor** |

## Investigations and diagnosis

The principal investigation is 'thyroid function tests', or TFTs for short:

- these primarily look at serum TSH and T4 levels
- T3 can be measured but is only useful clinically in a small number of cases
- remember that TSH and T4 levels will often be 'opposite' in cases of primary hypo- or hyperthyroidism. For example in hypothyroidism the T4 level is low (i.e. not enough thyroxine) but the TSH level is high, because the hypothalamus/pituitary has detected low levels of T4 and is trying to get the thyroid gland to produce more
- TSH levels are more sensitive than T4 levels for monitoring patients with existing thyroid problems and are often used to guide treatment
- Patients under treatment must be tested for TFT 6 weeks after dose change.

A number of thyroid autoantibodies can be tested for (remember the majority of thyroid disorders are autoimmune). The 3 main types are:

- Anti-thyroid peroxidase (anti-TPO) antibodies
- TSH receptor antibodies
- Thyroglobulin antibodies

There is significant overlap between the type of antibodies present and particular diseases, but generally speaking TSH receptor antibodies are present in around 90-100% of patients with Graves' disease and anti-TPO antibodies are seen in around 90% of patients with Hashimoto's thyroiditis.

## Other tests include:

- nuclear scintigraphy; toxic multinodular goitre reveals patchy uptake

## Thyroid function tests (TFTs)

The interpretation of thyroid function tests is usually **straightforward**:

| Diagnosis | TSH | Free T4 | Notes |
|---|---|---|---|
| Thyrotoxicosis (e.g. Graves' disease) | Low | High | In T3 thyrotoxicosis the free T4 will be normal |
| Primary hypothyroidism (primary atrophic hypothyroidism) | High | Low | |
| Secondary hypothyroidism | Low | Low | Replacement **steroid** therapy is required **prior** to thyroxine in pan -hypopituitarism. |
| Sick euthyroid syndrome (non-thyroidal illness) | Low | Low | Common in hospital inpatients T3 is particularly low in these patients, TSH may be normal in some cases<br>**rT3** is used to differentiate |
| Poor compliance with thyroxine | High | **Normal** | The TSH level is high. This implies that over recent days/weeks her body is thyroxine deficient.<br>However, the free T4 is within normal range.<br>The most likely explanation is that the **Pt. started taking the thyroxine properly just before the blood test.** This would correct the thyroxine level T4, T4 is converted to T3. But the TSH takes longer to normalise.<br>(**N** freeT4, **N** free T3, but ↑**TSH**) |
| **Sub-clinical hypothyroidism** | **High** | Normal | |
| **Steroid therapy** | **Low** | Normal | |
| **Sub-clinical hyperthyroidism** | **Low** | Normal | |

| Situation | TSH | fT4 | fT3 |
|---|---|---|---|
| Over-replacement with thyroxine | Low | High | Normal/High |
| Sick euthyroid syndrome | Normal/ High | Low | Normal/Low |
| TSH-secreting tumour | **High** | **High** | **High** |
| Untreated hypopituitarism | Low/Low normal | Low/Low normal | Low/Low normal |

## Treatment

This clearly depends on the cause. For patients with hypothyrodism thyroxine is given in the form of levothyroxine to replace the underlying deficiency.

**Patients with thyrotoxicosis may be treated with:**

- propranolol: this is often used at the time of diagnosis to control thyrotoxic symptoms such as tremor
- carbimazole: blocks thyroid peroxidase from coupling and iodinating the tyrosine residues on thyroglobulin → reducing thyroid hormone production. Agranulocytosis is an important adverse effect to be aware of
- radioiodine treatment

# Thyrotoxicosis

## Causes:

- **Graves' disease**: It accounts for **50-60% of cases of thyrotoxicosis**
- Toxic nodular goitre.
- Toxic adenoma (Plummer's disease)
- Thyroiditis
  - Subacute (de Quervain's) thyroiditis.
- Acute phase of Hashimoto's thyroiditis (later results in hypothyroidism)
  - Transient thyrotoxicosis in patients with early Hashimoto's disease resulting from the initial destruction of the thyroid gland and subsequent release of thyroid hormones.
  - **Positive thyroid peroxidase antibodies and negative TSH receptor antibody**
- **Secondary thyrotoxicosis:**
  - TSH-producing pituitary adenoma
  - **Ectopic TSH (e.g., struma ovarii, ovarian teratomas can produce exogenous TSH** causes secondary hyperthyroidism. can be visualized with a pelvic ultrasound or abdominal CT).
    - ➢ **Negative neck ultrasound and neck exam in the setting of hyperthyroidism** and low radioiodine uptake.

- Post-partum thyroiditis.
- Amiodarone therapy
- Thyrotoxicosis factitial

## Investigation:

- TSH down, T4 and T3 up.
- Thyroid and neck U.S including inferior thyroid artery.
- Thyroid autoantibodies (you can include anti-TSH antibodies).
- Other investigations are not routinely done but includes isotope scanning.

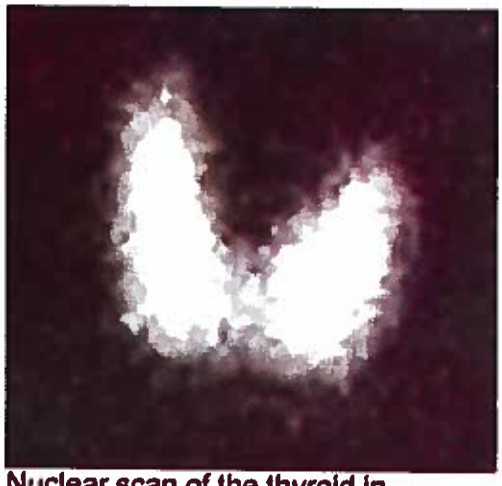
Due to the small risk of fetal abnormalities with carbimazole it is recommended to use PTU in the first trimester and then carbimazole in trimester 2+ 3.

A 1O weeks pregnant C/O anxiety and an inability to sleep. Blood results show: total thyroxine ($T_4$) 160 nmol/l (normal range 70-140 nmol/l), free $T_4$ 27 pmol/l (9-25 pmol/l) and thyroid-stimulating hormone (TSH) 0.2 mU/1. Which management of choice in this patient?

- **Observe and repeat thyroid function tests in one month**
- Diagnosis: Physiological hyperthyroidism

**MRCPUK part 1 exam: Pregnant lady investigated for excessive sweating and tremor. Blood tests reveal the following: TSH < 0.05 mu/l. T4 =188 nmol/1. What is the most aoorooriate management?** >> Propylthiouracil

This patient displays the following common findings of Graves disease: lid retraction and mild proptosis (exophthalmos), particularly evident on the left eye, and goiter.



Nuclear scan of the thyroid in Graves disease showing increased uptake (61%).

**N.B:** In a Pt. is started on carbimazole 20mg bid following a diagnosis of Grave's disease. What is the best biochemical marker to assess her response to treatment? >>> **TSH.** There is however a significant proportion of patients for whom TSH monitoring alone is insufficient. TSH may remain suppressed for several weeks (6 weeks) as continued production of thyroid stimulating immunoglobulins seen in Grave's disease reduces the need for the pituitary to secrete TSH.

**Factitious hyperthyroidism** is **rare** and it is important to **exclude** other causes before jumping to this conclusion. You can measure the **serum thyroglobulin**, which is **low** in factitious hyperthyroidism.
It is inappropriate abuse of thyroid hormone, ↓TSH, ↑FT4 with **NO** goiter, and **decreased** isotope thyroid scanning.
treatment: Psychological advice.

**NB:** Isolated **T3 thyrotoxicosis** (↓TSH, ↑FT3 with normal T4) is about **5%** of cases of thyrotoxicosis. Treatment: as usual.
The diagnosis of T3 thyrotoxicosis should be suspected in patients presenting with **symptoms of thyrotoxicosis** (including a goitre) in whom **serum T4 and fT4 are normal or low** with ↓ **TSH** and in whom the **RAIU is increased.**

**EX:** Pt with **thyrotoxicosis** with a diffuse goitre with **High level of all FT4, FT3 and TSH** >>> as the non-suppressed TSH suggests that this is due to **excessive TSH** production by the **pituitary** gland, the possibility of a **thyrotrope adenoma** (**TSH-oma**) must be pursued >>> **MRI pituitary.**

**Thyroid hormones: enhance all the following:**
- Insulin sensitivity (Insulin-dependent entry of glucose into cells)
- Myocardial oxygen consumption
- Nerve conduction
- Gluconeogenesis, and
- Oxidation of fatty acids.

# Graves' disease

- Graves' disease is **the most common cause of thyrotoxicosis.**
- It is typically seen in **women** aged **30-50 years.**
- Triggers: Physical or psychological stress and pregnancy

**Features:**

- Typical features of thyrotoxicosis
- Specific signs limited to Grave's (see below)

**Specific features** seen in **Graves'** but not in other causes of thyrotoxicosis:

- **Eye signs (only in 30% of patients):**
  - exophthalmos,
  - ophthalmoplegia.
- **Pretibial myxoedema.**
- **Thyroid bruit,**
- **Thyroid acropachy.**
  - digital clubbing
  - soft tissue swelling of the hands and feet
  - periosteal new bone formation

**Autoantibodies:**

- **Anti-TSH receptor stimulating autoantibodies** = (Often referred to as **Thyroid Stimulating Immunoglobulins) (90%).**
- **Anti-thyroid peroxidase (TPO) antibodies** (50%).

**Thyroid scintigraphy**

- diffuse, homogenous, increased uptake of radioactive iodine.

**NB**: **Anti-TSH receptor stimulating autoantibodies** is **specific** for **Graves'** disease and is present in the **vast majority** of cases.

**NB**: A **strong family history** of thyrotoxicosis is **typical** for Graves' disease.

**NB**: **Only** around **30%** of patients with Graves' disease have **eye** disease so the absence of eye signs does not exclude the diagnosis.

**NB**: **Only 50%** of patients with Graves' disease have positive antithyroid peroxidase (TPO) **antibodies**, and therefore their absence does not preclude the diagnosis.

**NB**: The absence of a goitre is also compatible with a diagnosis of Graves' (in addition, a goitre may not be detectable clinically, and may only be seen on imaging).

**NB**: **Graves'** thyrotoxicosis is associated with **pre-tibial myxoedema**, commonly described as **orange peel skin on both shins**. It is usually associated with: tachycardia, increased levels of SHBG, and **globally increased uptake on thyroid scan.**

**NB:** The most likely associate of Graves' disease is **vitiligo** occurring in approximately 7% of cases. It is important to appreciate that autoimmunity is relatively common in association with thyroid autoimmunity and include type 1 diabetes mellitus, Addison's, pernicious anaemia and Sjögren's.

**NB**: The D.D. for an **eye movement abnormality**, which cannot be explained by a single or multiple cranial nerve palsy is **myasthenia gravis** or **Graves' disease**.

**Myasthenia** is **unlikely** if **the patient can look up freely for long periods of time.**

**Graves' eye disease can occur with normal thyroid function (FT4 and TSH)**, so the diagnosis can be made by looking for **thyroid stimulating receptor antibody in the serum.**

**Graves' eye** disease **can occur in euthyroid, hypothyroid** or **hyperthyroid** setting.

The negative autoantibody argues against this being an autoimmune thyroiditis such as Graves' disease or hashitoxicosis.

## Management

options include titration of anti-thyroid drugs (ATDs, for example carbimazole), block-and-replace regimes, radioiodine treatment and surgery.

**Propranolol** is often **given initially** to block adrenergic effects.

**ATD titration:**

- Carbimazole is started at **40mg** and **reduced gradually** to maintain euthyroidism.
- Typically continued **for 12-18 months.**
- Patients following an ATD titration regime have been shown to **suffer fewer side-effects than** those on a block-and-replace regime.

## Carbimazole (CBZ) VS thiouracil (PTU)

| | Carbimazole (CBZ) | Proovlthiouracil (PTU) |
|---|---|---|
| **Action** | ↓ thyroid peroxidase | ↓ thyroid peroxidase + ↓$5^1$ deiodinase type 1 >> ↓ peripheral conversion of $T_4$ to $T_3$ |
| **Potency** | More (15 times as potent as (PTU) | **Less** |
| **Structure** | less protein bound, more transfer across placenta | more protein bound, less transferacross placenta |
| **Teratogenicity** | **Associated with aplasia cutis** | **Less associated with aplasia cutis** |
| **Major side effects** | **Aaranulocvtosis** | Hepatotoxicitv |
| **use in pregnancy** | **2nd and 3rd trimester** | **1st trimester** |

**Block-and-replace:**

- the major complication of carbimazole therapy is agranulocytosis
- Carbimazole is started at 40mg.
- **Thyroxine is added when** the patient is **euthyroid**.
- Treatment typically **lasts for 6-9 months.**
- Block-and-replace regimes should not be used in pregnancy

The major complication of **carbimazole** therapy is **agranulocytosis >>>**

**Treatment: Stop carbimazole** and **start PTU once** the neutrophils count has recovered with follow up CBC.

Carbimazole should be stopped if there is a demonstrable neutropenia/agranulocytosis with neutrophil count below 1.5 ×109/L (1.5-7).

Carbimazole-induced agranulocytosis >>> Carbimazole should be **withdrawn**, infection treated with appropriate **antibiotics** (broad spectrum cephalosporin) and occasionally, granulocyte colony-stimulating factor **(G-CSF)** is required when white count fails to respond.

NB: The incidence of leukopenia/neutropenia with carbimazole is **less than 1%**, so in any particular case **her TLC is normal with normal differential**, there is **no** requirement to stop carbimazole and she should be reassured **>>> Continue carbimazole and reassurance.**

**NB:** the effect of carbimazole has been potentiated by the liver **enzyme-inhibiting** effect of **erythromycin** that was prescribed for upper respiratory tract infection >>> so picture of more hypothyroidism.

## Radioiodine treatment:

- RAI is safe and that is why it is given across all ages as a definitive treatment of thyroxicosis.
- The **only indication** is toxic multinodular goiter (**TMNG**) or **a single toxic adenoma**.
- Patient should be advised that in the first fortnight there may be an exacerbation of her symptoms and that she will need regular follow up as she may become hypothyroid or her thyrotoxic symptoms may return.
- The most likely side effect of radioactive iodine is **hypothyroidism** with approximately **80%** developing hypothyroidism after therapy. It depends on the dose given, but as a rule **the majority of patient will require thyroxine supplementation after 5 years.**
- There is no evidence to suggest that RAI is associated with any cancers either thyroid neoplasia or gastric neoplasia.
- **Goitre shrinkage** may occur in only up to **30%** of cases following RAI.
- The risk of **recurrence** after anti-thyroid drugs is **above 50%.**
- **Contraindications:**
  - **Pregnancy** (pregnancy should be avoided for at least 4-6 months following ttt) and **breast feeding.**
  - **Age < 16 years.**
  - **Thyroid eye disease** is a relative contraindication, as it may worsen the condition.

## Surgery:

- There is some debate about whether sub-total or total thyroidectomy is the most appropriate option.
- With slow re-growth and the possibility of malignant change favoring total thyroidectomy, but this is countered with increased potential risk of post-operative hypoparathyroidism and RLN palsy.

Any patient with **large** goiter with **compression** symptoms and is **euthyroid (normal TFTs)**, so **anti-thyroid drugs and radioiodine would not be appropriate** and so the best choice option here is **thyroidectomy**.
**And also, in patients with ophthalmopathy.**

## Complications:

- **Transient hypo-parathyroidism** is said to occur in around **8%** of cases, with permanent hypoparathyroidism seen in 1-2% of patients undergoing thyroidectomy >>> **Hypocalcaemia >>> tetany.**

- **Infection** is seen in **1-2%** of patients undergoing thyroidectomy.
- **Bleeding** is less common, seen in around **0.5%** or less.
- **Superior laryngeal nerve palsy** affects **more** patients (**3-4%**).
- **Permanent recurrent laryngeal nerve (RLN) palsy** occurs in **1%**, the **inferior** thyroid artery runs closest to the recurrent laryngeal nerve.

Radioiodine therapy is the treatment of choice for patients with a relapse of Graves' disease in the absence of contraindications, such as pregnancy and active severe Graves ophthalmopathy

**Which structures is most closely related to the recurrent laryngeal nerve?**

- **Inferior thyroid artery**
- The superior thyroid artery runs closest to the superior laryngeal nerve.

## Toxic Multinodular Goitre (TMNG)

- Toxic multinodular goitre describes a thyroid gland that contains a **number of autonomously functioning thyroid nodules** that secrete excess thyroid hormones.
- Nuclear scintigraphy with technetium 99m reveals **patchy uptake**.
- **The treatment** of choice is **radioactive iodine (RAI) therapy.**

## Toxic adenoma (Plummer's disease):

### Treatment

#### Initial treatment

- Control symptoms with beta-blockers and thioamides until euthyroidism is achieved, followed by tapering of beta-blockers

#### Definitive treatment

- Non-pregnant, non-lactating adult **with no mass effect**:
  - **1st line >> Radioactive iodine therapy**
  - 2nd line >> subtotal thyroidectomy
- Non-pregnant, non-lactating adult **with mass effect**:
  - 1st line >> subtotal thyroidectomy
- Pregnant or lactating;
  - 1st line >> anti-thyroid drugs
  - 2nd line >> subtotal thyroidectomy

Lugol's iodine is used to gain rapid control of thyrotoxicosis prior to surgery.

**EX:** A 42-year-old man with a **thyroid mass**. He tells you that **his mother and brother** both suffered from **thyroid cancer**, his **BP** difficult to manage, his BP is 155/100 mmHg. There is a firm left sided thyroid mass, around 3 cm in diameter, Normal TSH, **High Ca** >>> The next step is **MRI Abdomen** >>> **exclusion of phaeochromocytoma is crucial before considering thyroidectomy.**

The history of thyroid carcinoma in two first degree relatives raises the possibility of a **familial thyroid cancer syndrome**. The hypercalcemia further increases suspicion that this **is medullary carcinoma of the thyroid**.

## Thyroid eye disease

Thyroid eye disease affects **between 25-50% of patients with Graves' disease.**

### Pathophysiology:

- It is thought to be caused by an **autoimmune** response against an autoantigen, possibly the **TSH receptor** → retro-orbital inflammation
- The inflammation results in **glycosaminoglycan and collagen deposition in the eye muscles.**

Bilateral exophthalmos that has been present for 5 years since patient was diagnosed with Graves disease. Although the radioactive iodine returned her thyroid function to normal, the exophthalmos continues to bother the patient.

Woman with unilateral Graves ophthalmopathy and vitiligo. There is a strong association between autoimmune thyroid diseases and vitiligo.

## Prevention:

- **Smoking** is the most important modifiable risk factor for the development of thyroid eye disease.
- **Radioiodine** treatment may increase the inflammatory symptoms seen in thyroid eye disease. In a recent study of patients with Graves' disease around 15% developed, or had worsening of, eye disease. **Prednisolone** may help reduce the risk.

Smoking is the most important modifiable risk factor for the development of thyroid eye disease.

## Features:

- The patient **may** be **euo-**, **hypo-** or **hyperthyroid** **at the time of presentation.**
- **Exophthalmos.**
- **Diplopia**
- **Conjunctival oedema.**
- Optic disc swelling.
- Ophthalmoplegia.
- Inability to close the eye lids, **lid lag**, and **lid retraction** may lead to sore, dry eyes. If severe and untreated patients can be at risk of exposure keratopathy.
- Lid lag and retraction are signs of stimulation of the sympathetic system as the thyroid hormones allow adrenaline to stimulate the receptors much effectively.

## Investigations

- Thyroid function tests: ↓ TSH and ↑ free T3/T4; ↑ TSH receptor antibodies
- **Noncontrast CT scan of the orbits:** **the initial image of choice**
  - assess the risk of future optic nerve compression by enlarged extraocular muscle at the orbital apex.
  - measure the of proptosis and retroocular fat accumulation
  - helpful in the differential diagnosis
- **MRI** of her orbits: certainly, demonstrate **retro-orbital and extraocular muscle inflammation.**

## Management:

- Topical lubricants and eye patches may be needed to help prevent corneal inflammation caused by exposure.
- **High dose steroids (prednisolone)** are the mainstay of initial therapy for thyroid eye disease.
- Orbital decompression surgery.
- Orbital radiotherapy (controversial).

**NB: Radioiodine exacerbate Graves's ophthalmopathy**, and patients with **pretibial myxedema** tend to have more severe ophthalmopathy.

### Monitoring patients with established thyroid eye disease:

For patients with established thyroid eye disease the following symptoms/signs should indicate the need for **urgent** review by an ophthalmologist (see **EUGOGO** guidelines): (**Eu**ropean **G**roup **o**n **G**raves' **O**rbitopathy):

- Unexplained sudden deterioration in **vision acuity**.
- Change in intensity or quality of **color** vision in one or both eyes.
- History of eye suddenly 'popping out' (**globe subluxation**).
- Obvious **corneal opacity**.
- Cornea still visible when the eyelids are closed.
- **Optic disc swelling**.

**NB: Graves' eye disease can occur with normal thyroid function (FT4 and TSH)**, so the diagnosis can be made by looking for **thyroid stimulating receptor antibody in the serum.**

## Thyroid storm

Thyroid storm is a **rare but life-threatening sudden** complication of thyrotoxicosis exacerbation.

It is typically seen in patients **with established thyrotoxicosis** and is rarely seen as the presenting feature.

**It is caused** by an exacerbation of hyperthyroidism often due to intercurrent illness,

- infection as pneumonia,
- trauma or emergency surgery.
- acute iodine load e.g. CT contrast media

**Iatrogenic thyroxine excess does not usually result in thyroid storm.**

### Clinical features include: (looks similar to pheochomocytoma)

- **fever > 38.5°C** with flushing: is the most characteristic feature.
- **Tachycardia**
- **Hypertension**
- Heart failure
- **Confusion**, agitation, **psychosis, seizures, coma**
- Nausea and vomiting
- **Abnormal liver function test**

## Investigations:

- Should look for underlying **precipitants.**
- **TFTs:** classically shows elevated T3 and T4, with **suppressed TSH.**
- **Liver** derangement (raised AST, ALT, LDH, ALP and bilirubin).
- **Renal** impairment,
- Elevated **CPK**
- **Electrolyte** imbalance (due to dehydration): ↓Na, ↓K,
- **Anaemia, thrombocytopenia, leucocytosis,**
- **Hypercalcaemia**, and
- **Hyperglycaemia.**

## Management:

- **Treatment should initially be of any underlying precipitating cause.**
- Resuscitation is then often required with oxygen, IV saline and a NGT if vomiting is dominant.
- Symptomatic treatment e.g., **paracetamol** (NOT aspirin as this can increase T4).
- **Anti-thyroid drugs:** e.g. carbimazole or **propylthiouracil (PTU).**
- **Lugol's iodine** (aqueous iodine) is then given after 4 hours
- **Propranolol** or diltiazem if propranolol is contraindicated
- **Dexamethasone** - e.g. 4mg IV qds - blocks the conversion of T4 to T3.
- **Chlorpromazine** can be used if there is severe agitation.
- **Treatment:** of heart failure and AF if present
- In severe cases exchange transfusion or **hemodialysis** may be required.

Untreated, such cases are usually fatal. Even with early diagnosis and treatment, the **mortality is 20-50% (some series 30-75%).**

Death may be caused by arrhythmia, CHF, hyperthermia or other unidentified factors.

### Thyrotoxic hypokalaemic periodic paralysis:

**EX:** A **26**-year-old **Chinese** man is admitted on the acute emergency take. He became very unwell after a squash game, complaining of **severe proximal limb weakness**. He has just started treatment for **thyrotoxicosis** (with carbimazole). He is **unable to get up off the bed** due to proximal weakness + **low Serum K** >>>> **Thyrotoxic hypokalaemic periodic paralysis.**

The prevalence of hypokalemic periodic paralysis is much higher in pts with thyrotoxicosis of **Chinese** origin versus Caucasians, (13-14% vs. 0.1-0.2%).

Attacks can **last from several minutes to hours**, and can be related to **exercise** or a significant carbohydrate load.

**Occasionally the respiratory and bulbar muscles may be involved.**

The history given is **too acute** to be either Guillain-Barre or myositis, with Guillain-Barre associated with weakness developing over a number of days, and myositis taking a more chronic course with muscle tenderness.

Without the presence of thyrotoxicosis, this picture would fit with **hypokalemic periodic paralysis.**

**EX:** A **55-year-old** man with a known history of **Graves'** disease presents to the ER with palpitations, anxiety and fine tremor of both hands.

ECG shows **rapid atrial fibrillation (AF)** with **ventricular rate of 160 to 180/min.** His blood pressure was 110/80 mmHg.

**TSH is low** 0.01 mU/l (N=0.4-5.0) and, **FT4 is high** 60.3 pmol/l (N=10-22).

The immediate management for this patient is >>> **Propranolol.**

**AF** occurs in **10% to 25%** of patients with hyperthyroidism, more commonly in **men** and the **elderly** than in women or patients less than 75-years-old.

Together with the other symptoms described it is generally caused by increased beta-adrenergic tone. **Propranolol is effective in controlling all symptoms** prior to initiation of specific therapy (e.g. carbimazole, which will have a more delayed effect on symptoms).

**Conversion** to sinus rhythm frequently **occurs spontaneously** with treatment of hyperthyroidism.

**Digoxin is very rarely effective alone**, but can be used in combination with propranolol if it is ineffective as a single agent.

Electric or pharmacologic cardioversion would only generally be attempted in patients who are haemodynamically unstable in whom other treatments have been unsuccessful.

AF is likely to **recur if** the underlying cause (i.e. hyperthyroidism in this situation) is not treated.

If AF persists, consideration should be given to anticoagulation in patients who are at risk of embolic events but this would not be the first treatment you would initiate.

## Subclinical hyperthyroidism

Subclinical hyperthyroidism is an entity which is gaining increasing recognition. It is defined as:

- Normal serum free thyroxine and triiodothyronine levels.
- With a **TSH below** normal range (usually < 0.1 mu/l).

### Causes:

- Multinodular goitre, particularly in **elderly females.**
- Excessive thyroxine may give a similar biochemical picture.

The importance in recognizing subclinical hyperthyroidism lies in the **potential effect** on the **cardiovascular system (AF or SVT)** and **bone metabolism (osteoporosis).**

It may also impact on quality of life and increase the likelihood of **dementia.**

### Management:

- TSH levels often revert to normal - therefore levels must be persistently low to warrant intervention.
- A reasonable treatment option is a **therapeutic trial of low-dose antithyroid agents for approximately 6 months** in an effort to induce a remission.

The American Association of Clinical Endocrinologists recommends that treatment is considered in patients with a persistently low TSH level if they are older than 65 years or are at risk of osteoporosis or heart disease.

## Subclinical hypothyroidism

**Subclinical hypothyroidism in a patient younger than 70:**
**TSH > 10mU/l >> Start levothyroxine replacement**
**TSH 4-10mU/l >> repeat the test in six months.**
**Subclinical hypothyroidism in a 70 year old patient:**
**Treat if TSH above 5.**

**Diagnosis:** TSH levels above the range but with normal levels of thyroxine {T4) and triiodothyronine (T3).

### Indications for treatment

- **TSH > 10 (below 70yrs-old).**
- Hypothyroid symptoms (regardless TSH level)
- Pregnancy or pregnancy planned in the near future

# Hypothyroidism

Hypothyroidism affects around 1-2% of women in the UK and is around 5-10 times more common in females than males.

## Symptoms & signs:

- cold intolerance, weight gain, increasing lethargy, constipation, coarse facial features,
- Skin
  - Dry (anhydrosis), cold, yellowish skin
  - Non-pitting oedema (e.g. hands, face)
  - Dry, coarse scalp hair, loss of lateral aspect of eyebrows
- Neurological
  - Decreased deep tendon reflexes
  - Carpal tunnel syndrome
- Gynaecological
  - Menorrhagia

## Primary hypothyroidism:

### 1) Primary atrophic hypothyroidism:

- **Most common cause** of hypothyroidism in UK.
- **Autoimmune disease**, associated with **IDDM**, **Addison's** or **pernicious anaemia.**
- 5 times more common in women

### 2) Hashimoto's thyroiditis:

- Autoimmune disease as above with goitre (positive microsomal antibodies)
- May cause transient thyrotoxicosis in the acute phase
- 5-10 times more common in women

### 3) After thyroidectomy or radioiodine treatment.

### 4) Drug therapy (e.g., lithium, amiodarone or anti-thyroid drugs such as carbimazole).

### 5) Dietary iodine deficiency.

**Iodine deficiency** is relatively common in parts of central **Africa**, where the **diet is poor in iodine** and access to **sea fish** is relatively difficult. It may present as **multi nodular goitre without** hypothyroidism, or in severe cases can progress to **frank** hypothyroidism.

Certain drugs are recognised to **interfere with absorption of thyroxine tablets**, these include **Rifampicin**, **Amiodarone**, **Calcium** supplements, **ferrous sulphate**, **cholestyramine**, **sevelamer** and **PPI (omeprazole)** >>> leading to a hypothyroid status (↑TSH).

## Secondary hypothyroidism (rare):

**From pituitary failure**

**Other associated conditions**

- Down's syndrome
- Turner's syndrome
- Coeliac disease

**N.B:** In European countries and UK >> **primary atrophic hypothyroidism** is the most cause causes of hypothyroidism, whereas in North America >> **Hashimoto's thyroiditis** appears to account for the majority of cases. The reason for this discrepancy is unclear.

**Hypothyroidism** is known to be associated with **hyper-carotenaemia**. It occurs because of a decrease in conversion from carotene to vitamin A. The consumption of vitamin A in hypothyroidism is also decreased.

**Other diseases associated with hypercarotenemia:** DM and Anorexia nervosa.

Any **female** patient with **weight gain**, **menorrhagia** and **dyslipidaemia** (↑**TG**) >>> Think of **hypothyroidism** (**Hashimoto's**). Once thyroxin is commenced, periods improve and hypertriglyceridemia usually begins to resolve.

**NB**: **Myxoedema coma** may be the **initial** presentation of hypothyroidism, but more usually occurs on background of long-standing disease with non-compliance on thyroxine replacement.

It is usually occurs in the **elderly** who are typically **non-compliant**.

Myxedema coma is a rare but very important to diagnose medical emergency.

The clues features are: 'yellowish hue' (referring to carotenaemia), obesity, bradycardia, hypothermia, and coma.

It carries a high mortality and should initially be treated with **IV thyroid hormone** - either T4 or T3 - and **IV hydrocortisone even** before results are obtained.

**Treatment**: **IV thyroxine** and **slow rewarming**, **BUT**

It is **very important to check co-existing hypoadrenalism by (↓Na, ↑K, ↓RBS, ↑BUN)** as in this case the ttt should be started **firstly with IV hydrocortisone** as giving thyroid hormone alone may worse an adrenal crisis.

# Hypothyroidism: management

## Key points:

- **Initial starting dose of levothyroxine should be lower in elderly patients and those with ischemic heart disease (e.g. 25-50 Mcg/day).**
- The BNF recommends that for patients with cardiac disease, severe hypothyroidism or patients over 50 years the initial starting dose should be 25mcg od with dose slowly titrated.
- Other patients should be started on a dose of 50-100mcg od
- Following a change in thyroxine dose thyroid function tests should be checked **after 8-12 weeks.**
- The therapeutic **goal** is **'normalization'** of the thyroid stimulating hormone **(TSH)** level.
- As the majority of unaffected people have a **TSH value 0.5-2.5 mU/l** it is now thought **preferable to aim** for a TSH in this range.
- There is no evidence to support combination therapy with levothyroxine and liothyronine.
- women with established hypothyroidism who become pregnant should have their dose increased 'by at least 25-50 micrograms levothyroxine'* due to the increased demands of pregnancy. The TSH should be monitored carefully, aiming for a low-normal value

## Side-effects of thyroxine therapy:

- Hyperthyroidism: due to over treatment
- Reduced bone mineral density
- Worsening of angina
- Atrial fibrillation

## Interactions

- iron, calcium carbonate
  - absorption of levothyroxine reduced, give at least 4 hours apart

*source: NICE Clinical Knowledge Summaries

# Hashimoto's thyroiditis (lymphocytic thyroiditis)

Hashimoto's thyroiditis is an **autoimmune** disorder of the thyroid gland.

**Hashimoto's thyroiditis = Hypothyroidism + Goitre + Anti-TPO**
**Hashimoto's thyroiditis is associated with thyroid lymphoma**

- It is typically associated with **hypothyroidism** or subclinical hypothyroidism although there may be a transient thyrotoxicosis in the acute phase.
- Early in the course of disease, T4 and TSH levels are normal and there are high levels of thyroid peroxidase antibodies and, less commonly, anti-thyroglobulin antibodies.
- Thyroid radioiodine uptake may be increased because of defective iodide organification, together with a gland that continues to trap iodine.
- It is 10 times more common in women.
- It is the most common hypothyroidism in UK, Irrespective of gender.

## Features: (3):

1) Features of **hypothyroidism** (or subclinical hypothyroidism).
2) **Goitre**: firm, **non-tender.**
3) **Anti-thyroid peroxidase Ab** (**Anti-TPO Ab**) (previously known as **thyroid microsomal autoantibodies**) and also **anti-Thyroglobulin antibody.**

## Associations

- other autoimmune conditions e.g. coeliac disease, type 1 diabetes mellitus, vitiligo
- Hashimoto's thyroiditis is associated with the development of **MALT lymphoma**

**Hashimoto's thyroiditis =**
**Hypothyroidism + Goitre + Anti-TPO Ab & Anti-TG Ab**

Hashimoto's thyroiditis is associated with thyroid **lymphoma**.

**Hashimoto's encephalopathy** which is extremely **rare**. You should suspect this as **elevated TSH** is present with **comatose patient** however there may be **no** clinical evidence of thyroid dysfunction.

It can result in altered mental state, myoclonus and ataxia.

It is a **steroid responsive** encephalopathy.

## Pendred's syndrome

Pendred is an autosomal recessive genetic disorder that is characterised by bilateral sensorineural deafness, with mild hypothyroidism and a goitre.

- The patients tend to present with progressive hearing loss and delay in academic progression.
- Often head trauma tends to make the **sensorineural deafness** worse, leading to patients having to avoid contact sports.
- In Pendred syndrome there is a defect in the organification of iodine, leading to dyshormonogenesis.
- However thyroid symptoms in pendred syndrome are often mild and patients are often clinically euthyroid, presenting only with a goitre.
- Thyroid function tests are also often normal, requiring the perchlorate discharge test to aid diagnosis.

### Diagnosis

- The syndrome can be diagnosed via **genetic testing** (Pendred syndrome **(PDS) gene, chromosome 7)**, audiometry and MRI imaging to look for **characteristic one and a half turns in the cochlea**, compared to the normal two and a half turns.

### Treatment

- thyroid hormone replacement
- cochlear implants.

## Sick euthyroid syndrome

In sick euthyroid syndrome (now referred to as **non-thyroidal illness**) it is often said that **everything (TSH, thyroxine T4 and T3) is low.**

- It is a very variable condition and many different pictures can be seen on thyroid testing. For this reason, it is often very difficult to interpret TFTs during intercurrent illness.
- **Mild reduction in TSH** during acute illness and increases during recovery.
- In the majority of cases however the **TSH level is within the normal range** (inappropriately normal given **the low thyroxine T4 and T3).**
- The primary abnormality is **decreased peripheral production of T3 from T4.**
- Reverse T3 (rT3) is made instead of normal T3.
- The patient will have an **increased reverse T3 (↑rT3)**, which can be measured.

- Secondary thyroid failure (pituitary causes) would be a differential, but measurement of **reverse T3** would help **differentiate** between this and sick euthyroid syndrome.
- **T4** is often normal or slightly low.
- Changes are **reversible** upon recovery from the systemic illness.
- Usually occurred in **hospitalized patient at ICU**, severe sepsis, heart failure, liver failure, renal failure, end-stage malignancy and starvation
- Thyroid replacement has **no** value and is a subject of **debate**.
- **appropriate repeat thyroid function tests in 3 months**

Usually no treatment is required, except to treat the underlying disease process.

Sick euthyroid syndrome >>> **TSH: normal or low, T4: low, T3: low**

## Thyroid cancer

**Features** of hyperthyroidism or hypothyroidism are not commonly seen in patients with thyroid malignancies **as they rarely secrete thyroid hormones.**

Risk factors for thyroid cancer include: Thyroid adenoma, endemic goiter, Hashimoto's thyroiditis lead to thyroid lymphoma), **FAP**, female, and exposure to radioiodine and radiotherapy.

There is **no screening tests for thyroid cancer**, but there are tests to detect recognised gene mutations.

If thyroid cancer is suspected >>> Thyroid US, scan and FNA.

Since **Thyroglobulin** is synthesized by well-differentiated thyroid carcinomas, it can serve as a useful tumour marker for assessment of **recurrence** of the tumour **but only after total thyroid ablation**.

there are five main types of thyroid carcinoma and their properties are given below:

| Cell type | Frequency | Behaviour | Spread | Prognosis |
|---|---|---|---|---|
| **Papillary** | 70% | **Often young females** present as "cold nodules" on isotope scanning | Local – sometimes bone / lung secondaries | **excellent** prognosis |
| **Follicular** | 20% | More common in females | Lung / Bone | **Good** if resectable |
| **Medullary cell** | 5% | **Often familial.** Cancer of parafollicular cells (c cell), **secrete calcitonin**, part of MEN-2 | Local and mets | **Poor**, but often very slow course |
| **Anaplastic** | <5% | Aggressive, Not responsive to treatment, can cause **pressure symptoms** | Locally invasive | **Very Poor** |
| **lymphoma** | 2% | *almost always non-Hodgkin lymphomas<br>* **Associated with Hashimoto's**<br>*often elderly women. | Locally invasive | **Poor** – but sometimes responds to radiotherapy |

**Gardener's syndrome:**
It is a **rare** familial **autosomal dominant** condition characterized by **multiple small** and **large** intestinal **polyposis** tumours + **Osteomas** + **soft tissue tumours** (multiple lipomas, fibromas, and epidermoid cysts).

It carries an increased risk of **papillary carcinoma of the thyroid**.

**Colonic carcinoma** develops in 7% of individuals by age 21 years, 50% by age 39 years and 90% by age 45 years.

**Colectomy** is recommended once polyps appear.

## Management of papillary and follicular cancer:

- **Total thyroidectomy.**
- **Followed by radioiodine (I-131)** to kill residual cells.
- **Follow up yearly with thyroglobulin levels** to detect early **recurrent** disease (only after total thyroid ablation).

Factors that suggest a **poor prognosis** in thyroid cancer include: **male sex**, increasing **age**, poorly differentiated histological features, and distant spread.

## Further information

| Type | Notes |
|---|---|
| Papillary carcinoma | • Usually contain a mixture of papillary and colloidal filled follicles<br>• Histologically tumour has papillary projections and pale empty nuclei<br>• Seldom encapsulated<br>• Lymph node metastasis predominate<br>• Haematogenous metastasis rare |
| Follicular adenoma | • Usually present as a solitary thyroid nodule<br>• Malignancy can only be excluded on formal histological assessment |
| Follicular carcinoma | • May appear macroscopically encapsulated, microscopically capsular invasion is seen. Without this finding the lesion is a follicular adenoma.<br>• Vascular invasion predominates<br>• Multifocal disease raree |
| Medullary carcinoma | • C cells derived from neural crest and not thyroid tissue<br>• Serum calcitonin levels often raised<br>• Familial genetic disease accounts for up to 20% cases<br>• Both lymphatic and haematogenous metastasis are recognised, nodal disease is associated with a very poor prognosis. |
| Anaplastic carcinoma | • Most common in elderly females<br>• Local invasion is a common feature<br>• Treatment is by resection where possible, palliation may be achieved through isthmusectomy and radiotherapy. Chemotherapy is ineffective. |

# Skin disorders associated with thyroid disease

### Skin manifestations of hypothyroidism

- dry (anhydrosis), cold, yellowish skin
- non-pitting oedema (e.g. hands, face)
- dry, coarse scalp hair, loss of lateral aspect of eyebrows
- eczema
- xanthomata

## Skin manifestations of hypothyroidism:

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- **Dry, coarse** scalp hair, loss of lateral aspect of eyebrows
- **Eczema**
- **Xanthomata**

**N.B: Pruritus** can occur in both **hyper**- and **hypo**thyroidism.

**Over replacement of thyroxine:** (↑ Free T4, still low TSH, Normal or high FT3)
This is **a very common** pattern of thyroid function tests. The main differential diagnosis is **subclinical hypo-thyroidism** and drug treatment with steroids, amiodarone or lithium.

**Overdoses of thyroxine (as suicidal tendency)** are relatively rare, and a number of strategies have been described in their management.
In reality, patients may be **partially protected** from thyroid hormone excess by production of **reverse T3.**
As such, the vast majority can be managed with regular **propranolol** to alleviate symptoms of tachycardia and anxiety.
In severe cases, **Plasmapharesis** to remove protein bound thyroxine, and **cholestyramine** to reduce enterohepatic circulation of thyroxine have been advocated.

The most likely investigation to differentiate between **self-administration of thyroid hormone** and **endogenous causes of thyrotoxicosis** is >>>> **Radioactive uptake thyroid scan.**

- Graves' disease is associated with diffusely increased radioactive uptake in the thyroid.

- A solitary hot nodule demonstrates increased uptake in one area, with decreased uptake elsewhere,

- Toxic multinodular goitre, multiple areas of increased uptake.

- In **thyrotoxicosis factitia**, uptake is **globally reduced**.

- Free T3, free T4 and thyroid binding globulin are **unhelpful** in determining whether thyrotoxicosis is due to exogenous administration of thyroid hormone or not.

**Thyroglobulin** is the **precursor** of thyroid hormones, therefore if undetectable, indicates an external source of thyroid hormone has been administered (Factitious thyrotoxicosis).

Also used for **follow up of recurrence** of thyroid tumour, only after excision.

So in **Factitious thyrotoxicosis: 1)** globally reduced radioactive uptake thyroid scan and **2)** Thyroglobulin is undetectable.

**McCune-Albright syndrome:**
It is due to a **mutation in a G-protein.**
This results in spectrum of **triad** of:
**1) Polyostotic fibrous dysplasia,**
**2) Café-au-lait spots** and
**3) Endocrinopathies (precocious puberty).**
It is established on clinical grounds, with the presence of increased risk of **bony fibromas** with **osteosarcoma** leading to possible multiple **pathological fractures** and **breast carcinoma** and **thyrotoxicosis.**

Thyroxine is mostly bound to thyroxine binding globulin in the circulation. **Estrogen therapy as in OCP** is associated with **elevation of thyroxine binding globulin** in the serum >>> Thus the total serum thyroxine may be misleading in this case, and **serum free thyroxine** will confirm whether this patient is hypothyroid or euthyroid.

So any patient on OCP >>> should test **free** not total T4.

Heparin is having an "in vitro" effect on thyroxine (T4) levels.

**IV heparin** interferes with the thyroid function tests assay on occasions displacing bound thyroid hormone >>> ↑ **Free T4** with normal TSH.

Early bilateral pretibial myxedema in a patient with Graves eye disease. These asymmetrical erythematous plaques and nodules

Pretibial myxedema in a patient with Graves ophthalmopathy. Hair follicles are prominent, giving a peau d'orange appearance.

## Congenital hypothyroidism

Congenital hypothyroidism affects around 1 in 4000 babies. If not diagnosed and treated within the first four weeks it causes irreversible cognitive impairment

### Features

- prolonged neonatal jaundice
- delayed mental & physical milestones
- short stature
- puffy face, macroglossia
- hypotonia

Children are screened at 5-7 days using the heel prick test

## Subacute (De Quervain's) thyroiditis

Subacute thyroiditis (also known as **De Quervain's thyroiditis**) is thought to occur **following viral infection (preceded with flu-like symptoms)** and typically presents with **hyperthyroidism.**

Flu-like illness is followed by transient hyperthyroidism, then hypothyroidism, then recovery.

It is probably viral in origin, and results in release of T3 and T4 into the circulation in large quantities. As the condition resolves patients become hypothyroid and then euthyroid.

Thyrotoxicosis is related to **increased release of stored thyroid hormone** rather than increased production of thyroid hormone. As such carbimazole and propylthiouracil are ineffective.

The hypothyroid state may become permanent in 5-10% of patients, but the vast majority go onto to the recovery phase with euthyroid status.

The symptoms of hyperthyroidism will resolve but can take weeks to a few months to do so, and so thyroid status should be monitored.

**It is associated with HLA-B35** and it is thought that a viral antigen binds to HLA-B35 molecules on macrophages.

### Features:

- **Hyperthyroidism.**
- **Painful tender goitre.**
- **Raised ESR** (around 40- 80 but this is not specific)
- **Globally reduced uptake on radioactive iodine (RAI 131 scan).**

## Management:

- **Usually self-limiting - most patients do not require treatment**
- Thyroid pain may respond to **aspirin** or other **NSAIDs.**
- In more severe cases **steroids** (**prednisolone** 30-40 mg/day) are used, particularly if hypothyroidism develops. Prednisolone can be stopped when T4 normalizes.
- **βB** help control the tremor and anxiety associated with thyrotoxicosis (Propranolol is the most appropriate treatment for her transient symptoms of hyperthyroidism).
- Anti-thyroid drugs have **NO** value in the management of the condition as the excess circulating thyroid hormone is due to the **release of the pre-existing thyroid hormone** as a result of **follicular damage** rather than from increase synthesis.
- If hypothyroidism occurs in the late stages, give thyroid replacement therapy guided by TSH levels.

**(RAI 131 scan):**
- In **Graves'** disease >>> you would expect **homogenous** high uptake,
- Whereas a **toxic nodule** >>> would show a **solitary** area of high uptake.
- In Subacute (De Quervain's) thyroiditis >>> **No** uptake (minimal up to zero uptake).

**Antibodies** such as TSH receptor antibodies and TPO are found only in **autoimmune** thyroid disease.

# Riedel's thyroiditis

**Riedel's thyroiditis is a rare cause of hypothyroidism**

- characterised by dense fibrous tissue replacing the normal thyroid parenchyma.
- On examination a hard, fixed, painless goitre is noted.
- It is usually seen in middle-aged women.
- It is associated with retroperitoneal fibrosis.
- Riedel's thyroiditis is often confused with thyroid carcinoma.

## Treatment

- **Steroids** and **tamoxifen** to inhibit connective tissue proliferation.
- **wedge resection of the thyroid isthmus** to alleviate tracheal obstruction is still the preferred surgical therapy

# Pregnancy and thyroid problems

In pregnancy there is a **twofold increase in the levels of thyroxine-binding globulin (↑TBG) this is due to a combination of ↓ hepatic clearance of TBG and ↑ synthesis in response to oestrogen.**

The ↑ TBG **plateaus** at **20 weeks** and **then gradually falls.**

This causes an **increase in total thyroxine T4** level but does **not** affect the free thyroxine level.

In pregnancy: **Normal** TSH, **Normal** free T3, **Normal** free T4 , **BUT high total** T3 and **high total** T4 due to increase in the binding Globulin level.

It is a feature of normal pregnancy that **T3** and **T4** show **slight increase** just above the normal range in **first** trimester, with **slight suppression** of **TSH** just below the normal range in up to **15%** of pregnancies during the first trimester & **5%** of pregnancies in the second trimester, this is due to the partial thyroid stimulating action of **β-HCG** and this is a normal variant >>> **observe** and **follow up TFTs. (It is mimic hyperthyroidism, but NO need for PTU).**

**Slightly elevated thyroid hormones FT3 & FT4** with **slightly suppression of TSH** may be considered a **normal variant** in the **early** stages of pregnancy especially if there is a history of **hyperemesis** due to **HCG** effect >>> ttt just **observe.**

**TSH falls** in the **first** and **second** trimester, and **increases** in the **third** trimester with **subsequent fall in free T4 and T3 in the third trimester.**

**TSH**: in **first** and **second** trimester >>> **Low TSH** especially with **hyperemesis,**

But in **Third** trimester >>>> ↑ **TSH** >>> **so, low FT3 and low FT4.**

## Thyrotoxicosis

**Untreated thyrotoxicosis** increases the risk of **fetal loss**, **maternal heart failure** and **premature labour.**

**Graves' disease is the most common cause of thyrotoxicosis in pregnancy.** It is also recognized that activation of the TSH receptor by HCG may also occur - often termed **transient gestational hyperthyroidism.** HCG levels will fall in 2nd and 3rd trimester.

## Management:

- **Propylthiouracil (PTU): 50 mg TDS up to 150 mg BID (50-300 mg/day)** has traditionally been the antithyroid drug of choice in pregnancy. This approach was supported by the 2007 Endocrine Society consensus guidelines. **It is more highly protein bound than carbimazole and so less transmitted to fetus cross the placenta. It also has the advantage of being excreted to a lesser extent than carbimazole in breast milk.**
- Due to the **small risk** of fetal abnormalities with **carbimazole** it is recommended to use **PTU in the first trimester** during organogenesis and **then carbimazole in the 2nd and 3rd trimester.**
- Women who are taking carbimazole and learn they are pregnant should be switched to PTU at the time of the positive pregnancy test.
- **Maternal free thyroxine levels (Free T4)** should be **kept in the upper limit of the normal** reference range **to avoid fetal hypothyroidism.**
- **Thyrotrophin receptor stimulating antibodies** should be checked at 30-36 weeks gestation - helps to determine risk of neonatal thyroid problems.
- **Block-and-replace regimes should not be used in pregnancy** as carbimazole crosses the placenta but thyroxine does not, so the block and replace regimen approach could render the neonate profoundly hypothyroid.
- Radioiodine therapy is contraindicated as it would also be taken up by the fetal thyroid.
- Propranolol would ameliorate the symptoms but may impact upon the fetus.
- Lithium is contraindicated in pregnancy as is potassium perchlorate.
- During lactation: the infant's thyroid function should be monitored, although levels in milk are likely too small to affect the infant.
- **Patient with hyperemesis gravidarum usually has hyperthyroidism**: the emesis is usually driven by high levels of **beta-HCG**. Beta-HCG has a degree of **thyroid stimulating activity**. In the circumstances it is likely that this has **driven TSH down** to below the lower limit of normal. No intervention is necessary, and there is **no** value in using anti-thyroid drugs in this situation.

## Hypothyroidism:

### Key points:

- **Thyroxine is safe during pregnancy.**
- **Serum TSH** measured **in each trimester** (at 6-8 weeks, and then at 16-20 weeks and 28-30 weeks) and **6-8 weeks post-partum.**

- **Some women require an increased dose of thyroxine during pregnancy.**
- Average increase in thyroxin requirements is **25-50 Mcg** and this increased need ceases immediately after delivery.
- If the patient is **stable** with regard to **thyroxine dose pre-pregnancy** then they are likely **to remain stable without any dose adjustment during the pregnancy.**
- Thyroxine treatment should be altered according to the **free T4** levels as TSH may remain elevated even with appropriate treatment (especially in the third trimester).
- **Breast feeding is safe whilst on thyroxine**

## Post partum thyroiditis

It is a variant of chronic autoimmune thyroiditis (**Hashimoto's** thyroiditis).

The exact etiology is unknown but lymphocytic infiltration of the thyroid is typical, suggesting auto-immunity.

Post-partum thyroid dysfunction is said to occur in up to **10%** of women during the **first year after delivery.**

It is **characterized** by the presence of **anti-microsomal (Anti-TPO antibodies)** in **30-52% of cases.**

Histologically: **destructive lymphocytic thyroiditis.**

It tends to occur **within the 4 months of delivery** by **transient hyperthyroidism**, followed by a **hypothyroid** phase at 3 to 6 months, followed by **spontaneous recovery** in **one third** of cases within 6-12 months of delivery, **although around 40% eventually go on to develop permanent hypothyroidism.**

It can present with transient hyperthyroidism, but more women present during the **hypothyroid** stage (↑ **TSH).**

The commonest symptom is **fatigue (tiredness/lethargy).**

In **rare** cases thyrotoxicosis may be associated with **psychotic** presentation (she is convinced that her husband is trying to poison her) (D.D. Postnatal depression).

**PPT: Hyper >>> Hypo >>> spontaneous recovery (1/3) or permanent hypo (40%)**

In the remaining two-thirds, a single-phase pattern or the reverse occurs.

## Management:

- It is centred on **symptomatic treatment** using **beta-blockers (Propranolol 20 mg TDS)** for relief of tremor or anxiety, and observation for the development of persistent hypo- or hyperthyroidism.
- In patients with **post-partum hypothyroidism**, **low dose thyroxine 50 Mcg** may be used to allow for spontaneous recovery to occur with re-checking of thyroid function off therapy after 6 months of ttt.

**EX**: A 25-year-old woman, she is **10 weeks post-partum** and has been generally unwell for 2 weeks with malaise sweats, **tiredness** and anxiety.
On examination she is hemodynamically stable, and clinically euthyroid.
TFTs show the following: ↑ FT3, ↑FT4, Low TSH & +ve Anti TPO antibodies.
It is **postpartum thyroiditis**
The appropriate management is **propranolol** (**NOT** carbimazole or PTU)

# Adrenal gland disorders

## Adrenal gland

**Adrenal cortex mnemonic: GFR – ACD**

### Adrenal cortex (mnemonic GFR - ACD)

- Zona Glomerulosa (outside): **Mineralocorticoids**, mainly **Aldosterone**
- Zona Fasciculata (middle): **Glucocorticoids**, mainly **Cortisol**
- Zona Reticularis (inside): **Androgens**, mainly **DHEA** (Dehydroepiandrosterone)

### Adrenal medulla

**The adrenal medulla secretes**

- **all the adrenaline in the body**
- Small amounts of noradrenaline.

**It essentially represents an enlarged and specialised sympathetic ganglion**

### Nnoradrenaline metabolism

**The action of noradrenaline released at sympathetic nerve endings is terminated by which mechanism?**

- The majority are **Re-uptaked by the axonal terminals** >> **into the neurosecretory granules**
- small amount is metabolised by monoamine oxidase (MAO).
- smaller quantities that escape into the circulation are metabolised by catechol-O-methyl transferase (COMT).

## Dehydroepiandrosterone sulphates (DHEAS)

### Overview

- The most abundant circulating adrenal steroid.
- **Hormone class:** Androgen
- **Production site:** Zona reticularis of the adrenal cortex
- **Function:** Substrate in estrogen and testosterone synthesis: DHEA >> converted to estrogen and testosterone in peripheral tissue. Most of the DHEA is converted to **androstenedione.**
- **Regulation of secretion:** CRH >> ↑ secretion of ACTH in the pituitary gland >> ↑ secretion of androgens in the adrenal cortex
- Decline with age

## Clinical significance

- DHEAS is secreted exclusively by the adrenal glands and is therefore a good marker for adrenal androgen production.
- A mildly elevated DHEAS *level* is common in women with PCOS. In contrast, DHEAS values above 700 ng/dl (7µg/ml, 18umol/L) are suggestive of adrenal neoplasm.
- Loss of functioning adrenal tissue as in Addison's disease may result in symptoms secondary to **androgen deficiency,** such as loss of libido.
- A trial of **dehydroepiandrosterone (DHEA)** is recommended in **women** with primary adrenal insufficiency who have **low libido, low energy** levels, or **depressive** symptoms despite glucocorticoid and mineralocorticoid replacement >> **increasing a sense of wellbeing**

**Exam: Addison's disease C/O a decrease in her libido. On examination there is a slight loss of ubic hair. What is the most likel cause? >> Deh droe iandrosterone DHEA deficienc**

# Cortisol

## Overview

- Hormone class: Glucocorticoids
- Production site: Zona fasciculata of the adrenal cortex
- Regulation of secretion: CRH >> ↑ secretion of ACTH in the pituitary gland >> ↑ secretion of glucocorticoids in the adrenal cortex
- Plasma cortisol levels in normal individuals show a circadian rhythm.
- **Levels are highest in the early morning and fall to their lowest levels during sleep at around midnight.**
- **At what time of day is a random cortisol test most likely to be abnormal?**
  - **2400 hours**

## Function

**Metabolism:** Cortisol plays an important role in the mobilization of energy reserves.

- ↑ Gluconeogenesis to maintain blood glucose levels
- ↑ Glycogen synthesis to maintain glucose storage
- ↑ Protein catabolism
- ↑ Lipolysis

- ↑ Appetite
- ↑ Insulin resistance

**Immune system:** anti-inflammatory and immunosuppressive effects (see "Pharmacodynamics of glucocorticoids")

**Wound healing:** fibroblast inhibition >> ↓ collagen synthesis >> ↓ wound healing

**Blood pressure:** mild mineralocorticoid effect (stimulation of aldosterone receptors in high concentrations) and ↑ potassium excretion >> ↑ blood pressure

To remember the effects of cortisol, think "**A BIG FIB**": increased **A**ppetite, **B**lood pressure, **I**nsulin resistance, **G**lucose production, and decreased **F**ibroblasts, **I**mmunity, and **B**one formation.

## Cortisol levels are increased in:

- **pregnancy**
- conditions of physical and emotional stress
- oestrogens
- oral contraceptives
- amphetamines
- cortisone
- spironolactone.

**What is the immediate precursor in the production of cortisol?**
**>> 11-Deoxycortisol**

**No need to evaluate cortisol secretion in critically ill patients**

- In a critically ill patient **CRH, ACTH** and cortisol levels increase rapidly as a haemostatic response to the illness.

  acute illness >> ↓ cortisol binding globulin and albumin >>↑ free cortisol levels (not truly reflective of adrenal hypersecretion)

# Aldosterone

## Overview

**Hormone class:** Aldosterone is the major circulating mineralocorticoid

**Production site:** zona glomerulosa of the adrenal cortex.

**Action:** ↑ Na+ reabsorption >> water reabsorption and K+ secretion into the urine >> ↑ blood pressure, hypokalemia, and ↑ pH level.

**Site of action:** principal site: **distal renal tubule**

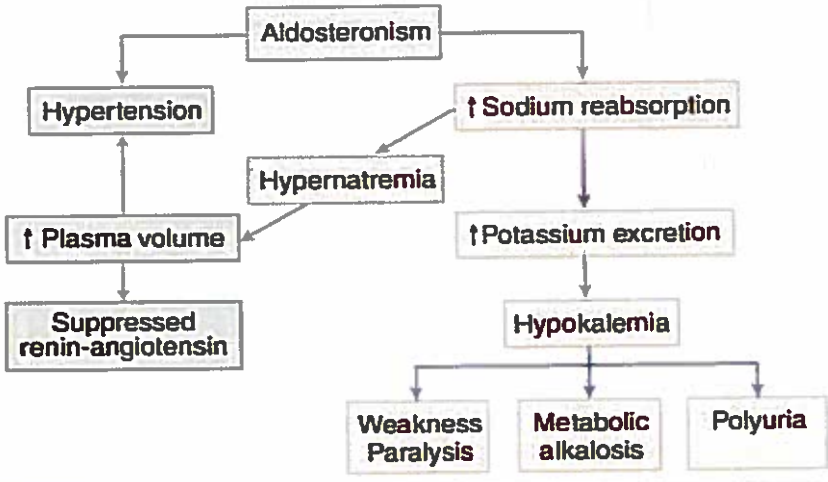
**Regulation** of synthesis and secretion:

### Stimulators

- Hypovolemia -->↓ renal perfusion (e.g., due to hypotension, stimulation of β1 receptors in the kidney) >> triggers renin release >> promotes the conversion of angiotensinogen (produced in the liver) to angiotensin I (AT I) , AT I is turned into angiotensin II via angiotensin-converting enzyme (highest concentration in the lungs where it is produced by vascular endothelial cells). Angiotensin II causes vasoconstriction and triggers the secretion of aldosterone.
- **Hyperkalemia**

### Inhibitors

- Principle inhibitors
  - Hypervolemia
  - Hypokalemia
- Negative feedback: ↑ systemic arterial blood pressure >> ANP release from atrial myocytes >> inhibition of renin release >> vasodilation, natriuresis, and ↑ diuresis



# Adrenal hyperandrogenism

## Causes

### Primary adrenal diseases

- Premature adrenarche
- Adrenal tumors (adenomas, carcinomas, bilateral macronodular adrenal hyperplasia)

### ACTH hypersecretion

- Congenital adrenal hyperplasia (CAH)
- ACTH-dependent Cushing's syndrome
- Glucocorticoid resistance
- Cortisone reductase deficiency

### Hyperprolctinemia

### Exogenous

- Androgens

## Features

- Virilization: the appearance of male secondary sexual characteristics in a female individual
- Hirsutism: excessive male pattern hair growth (e.g., chin, upper lip, mid-sternum, abdomen, back, buttocks)
- Male-pattern hair loss
- Acne
- Increased muscle mass
- Voice deepening
- Clitoromegaly
- Rapid onset of virilization is suggestive of exogenous androgen intake or androgen- secreting tumors

### Differential diagnosis of hyperandrogenism in females

| Diaanosis | Characteristic findina |
|---|---|
| PCOS: Most common (75-80% of cases) | Polycystic ovaries on pelvic ultrasound |
| Nonclassic CAH | ↑ 17-Hydroxyoroqesterone |
| Conqenital adrenal hyperplasia | Ambiquous qenitalia |
| Cushinq disease | ↑ 24-hour urine free cortisol |
| Hypothyroidism | ↑ TSH |
| Androgen-secreting tumor (e.g., Sertoli-Leydig cell tumor, adrenal) | ↑ DHEA-S (> 700 µg/ dl) |

# Premature adrenarche

## Definition and pathophyslology

- Premature maturation of the adrenal zona reticularis (adrenarche)->> ↑ androgen levels >> **onset of pubarche before age 8 years in girls and age 9 years in boys.**

## Associated conditions

- Associated with obesity, insulin resistance, and later development of PCOS and/or metabolic syndrome

## Epidemlology

- **Most common cause of precocious pubarche**
- ♀>♂

## Features

- Precocious pubarche: onset of pubic and/or axillary hair growth < 8 years in girls and < 9 years in boys
- Adult-type body odor
- Seborrhea, acne
- Increased height for age with a linear growth rate
- Other secondary sexual characteristics are absent (No breast development or testicular enlargement, or frank virilization.)

## Diagnosis

- ↑ Serum androgen concentrations (DHEA-S, testosterone)
- Advanced bone age

## Differential diagnosis

### Idiopathic premature pubarche

- Premature onset of pubarche most likely due to increased sensitivity of the pilosebaceous units to normal levels of androgen
- No biochemical evidence of adrenarche (i.e., normal serum androgen concentrations)
- Normal bone age

**Treatment:** No treatment is needed besides reassurance.

# Corticosteroids

Corticosteroids are amongst the most commonly prescribed therapies in clinical practice. They are used both systemically (oral or intravenous) or locally (skin creams, inhalers, eye drops, intra-articular).

They augment and, in some cases, replace the natural glucocorticoid and mineralocorticoid activity of endogenous steroids.

The relative glucocorticoid and mineralocorticoid activity of commonly used steroids is shown below:

| **Minimal glucocorticoid activity, Very high mineralocorticoid activity,** | **Glucocorticoid activity, high mineralocorticoid activity,** | **Predominant glucocorticoid activity, low mineralocorticoid activity** | **Very high glucocorticoid activity, minimal mineralocorticoid activity** |
|---|---|---|---|
| Fludrocortisone | Hydrocortisone | Prednisolone | Dexamethasone<br>Betamethasone |

This is clinically relevant as there are some situations where it is important to combine high glucocorticoid (anti-inflammatory) activity with minimal mineralocorticoid (fluid-retention) effects. A good example is the use of **dexamethasone** for patients **with raised intracranial pressure** secondary to **brain tumours**.

## Side-effects:

The side-effects of corticosteroids are numerous and represent the single greatest limitation on their usage. Side-effects are more common with systemic and prolonged therapy.

## Glucocorticoid side-effects:

- **Endocrine:** impaired glucose regulation, increased appetite/weight gain, hirsutism, and hyperlipidaemia.
- Cushing's syndrome: moon face, back hump, striae.
- **Musculoskeletal:** **proximal myopathy**, **osteopenia** and **osteoporosis** rather than osteomalacia, **avascular necrosis** of the femoral head. **(Osteoporosis >>> which leads to Vertebral collapse).**
- **Immunosuppression:** increased susceptibility to severe infection, reactivation of tuberculosis.

- **Psychiatric:** insomnia, mania, depression, psychosis.
- **Gastrointestinal:** peptic ulceration, acute pancreatitis.
- **Ophthalmic:** glaucoma, cataracts.
- Suppression of growth in children.
- Intracranial hypertension
- **dermatological:** acne
- **neutrophilia**

## Mineralocorticoid side-effects:

- Fluid retention.
- Hypertension.

## Selected points on the use of corticosteroids:

- **Patients on long-term steroids** should have their doses **doubled** during **intercurrent illness**.
- The BNF suggests **gradual withdrawal** of **systemic** corticosteroids if patients have: received **more than 40mg prednisolone daily** for **more** than **one week**, received more than 3 weeks treatment or recently received repeated courses.

Patients on long-term steroids should have their doses **doubled** during **intercurrent illness**.

**Proximal myopathy**, **easy bruising** and **thin skin** are clinical features that are **most suggestive of Cushing's syndrome**.
Otherwise, abdominal striae, back hump, and acanthosis nigricans are all features of obesity.

**Corticosteroids** are recognized to **inhibit osteoblast activity** and **increase osteoblast apoptosis**. This is thought to be a more important component in bone loss with respect to **steroid induced osteoporosis** versus any effect on osteoclasts.

Patients taking **7.5 mg or more of prednisolone daily for 3 months or longer** should be offered **osteoprotection**.

The most appropriate therapy advocated by the National Osteoporosis Society for the **prevention of steroid-induced osteoporosis** would be **bisphosphonate** therapy such as Didronel or alendronate.

These are the **only class** of drug shown to offer osteoprotection with steroid therapy.

**EX:** 26-year-old male **body builder** + **azoospermia** + Lab: **low FSH** and **low LH** but with **normal testosterone**.
The most likely diagnosis is **steroid-induced hypogonadism**.
**Body builders** may be involved in the illicit use of **anabolic and androgenic steroids**. These results are consistent with ongoing use of androgens. The hypogonadism if persistent may be **treated with human chorionic gonadotropin (HCG).**

## Hyperaldosteronism: Overview

**Definition:** Increased secretion of aldosterone from adrenal gland.

**Features and complications**

- Hypertension
  - ↑ Aldosterone >> ↑ open Na+ channels in the cortical collecting ducts of the kidneys >> ↑ Na+ reabsorption and retention >> water retention >> hypertension
- ↓ or normal K+
  - may be normal in up to 50% of cases
  - Diabetes insipidus: hypokalaemia >> desensitization of renal tubules to antidiuretic hormone (ADH) >> polyuria and polydipsia
- Metabolic alkalosis
  - ↑ H+ secretion in the kidney in order to enable ↑ K+ reabsorption
- ↑ Aldosterone >> reduce nitric oxide bioavailability >> ↓ endothelium-dependent vasodilatation >> ↑ risk of cardiovascular events.
- ↑ Aldosterone >> ↑ collagen synthesis >> promotes myocardial fibrosis and cardiac remodeling >> ↑ myocardial stiffness and ↑ left ventricular mass >> ↑ risk of ventricular arrhythmias and sudden cardiac death.
- 1° hyperaldosteronism does not directly cause edema due to aldosterone escape mechanism. However, certain 2° causes of hyperaldosteronism (eg, heart failure) impair the aldosterone escape mechanism, leading to worsening of edema.

**Aldosterone escape**

- Inappropriately elevated aldosterone >> sodium and water retention >> volume expansion >> secretion of atrial natriuretic peptide (ANP) and pressure natriuresis >> **compensatory diuresis >> "escape" from edema formation and hypernatremia**
- In edematous disorders the aldosterone escape mechanism is impaired, resulting in worsening edema.

## General causes of hyperaldosteronism

### Primary hyperaldosteronism

- Due to **bilateral adrenal hyperplasia** (most commonly) and adrenal adenoma (Conn's syndrome) (less commonly)
- ↑ aldosterone >> ↓ renin >> ↑ aldosterone to renin ratio (ARR).

### Secondary hyperaldosteronism

- Due to renovascular hypertension, fibromuscular dysplasia, juxtaglomerular cell tumors (renin- producing), and oedema (eg, cirrhosis, heart failure, nephrotic syndrome).
- The **raised aldosterone level is driven by raised renin levels.**
- ↓ blood flow to the kidneys (e.g. due to renal artery stenosis, heart failure, and cirrhosis). >> ↓ renal perfusion >> ↑ renin >> ↑ aldosterone (aldosterone to renin ratio (ARR) will be normal).

## Primary hyperaldosteronism (Conn's syndrome)

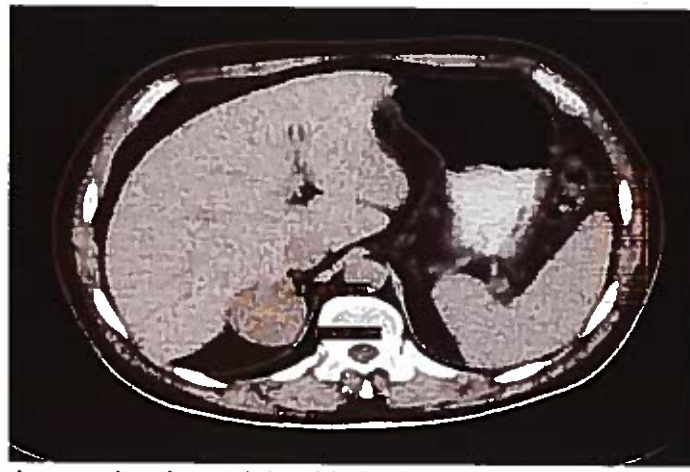
It accounts for up to 10% of all hypertensive patients.
It is the most prevalent form of secondary hypertension.

It is now recognized as a common secondary cause of hypertension.

Primary hyperaldosteronism was previously thought to be most commonly caused by an adrenal adenoma, termed Conn's syndrome.

As the name suggests, **aldosterone levels are high** so this **suppresses renin levels**.

However, recent studies have shown that **bilateral idiopathic adrenal hyperplasia** is the cause in **up to 70% of cases**.



CT abdomen showing a right-sided adrenal adenoma in a patient who presented with hypertension and hypokalaemia. The adenoma can be seen 'next to' or 'below' the liver.

Differentiating between the two is important as this determines treatment.

Adrenal carcinoma is an extremely rare cause of primary hyperaldosteronism.

**Bilateral idiopathic adrenal hyperplasia** is the most common cause of primary hyperaldosteronism.

## Consider testing patients with:

- **Stage 1** hypertension (>160-179/100-109 mmHg).
- **Stage 2** hypertension (>180/110 mmHg).
- Drug resistant hypertension.
- Hypertension and spontaneous or diuretic-induced hypokalaemia.
- Hypertension with adrenal incidentaloma.
- Hypertension and a family history of early onset hypertension or cerebrovascular accident at a young age (less than 40-years-old).
- Hypertensive first-degree relatives of patients with primary hyperaldosteronism.

## Features: (↑ Aldosterone >> Na absorption, excrete K and H):

- **HTN**
- **Hypokalemia**
  - e.g., muscle weakness
  - this is a classical feature in exams but studies suggest this is seen in only 10-40% of patients
- **Alkalosis**
- **Hypernatremia**

## Investigations:

- the 2016 Endocrine Society recommend that a plasma **aldosterone/renin ratio is the first-line investigation** in suspected primary hyperaldosteronism
  - should show high aldosterone levels alongside low renin levels (negative feedback due to sodium retention from aldosterone)
- following this a high-resolution CT abdomen and adrenal vein sampling is used to differentiate between unilateral and bilateral sources of aldosterone excess
  - if the CT is normal adrenal venous sampling (AVS) can be used to distinguish between unilateral adenoma and bilateral hyperplasia

## Aldosterone-to-renin ratio (ARR): Approach

### Eliminate confounding factors before testing

- Correct hypokalemia (because low potassium suppresses aldosterone secretion)
- Encourage normal salt intake (do not restrict salt intake)
- Discontinue agents known to affect **ARR** and use an alternative agent.
  - Drugs need to be stopped: **ACEi, ARB, diuretics, and β-blockers** for 2 weeks (wash-out period) and **spironolactone** for 6 weeks.
  - alternative agent which can be used: **Alpha-blockera (e, g, doxazosin), calclum channel blocker, (e.g. amlodipine) and Hydralazine**
  - Although **ACEi** are associated with false negative test results, **in clinical practice** the **ARR** can be assessed without stopping these agents. In fact, **ACEi may** actually **improve the sensitivity of the test.**
  - **Alpha blockers such as doxazosin have the lowest effect on the renin- angiotensin system**

**The blood sample should be taken in the morning during standing position** (i.e., with the patient standing for 2 h)

- Values obtained in the upright position are more sensitive than supine test results.
- **aldosterone is usually higher when the patient is erect than when supine (in bilateral hyperplasia)**

### Positive screening tests

- Confirm diagnosis (e.g., oral sodium loading test or saline infusion test)
- Identify subtype and etiology (e.g., via imaging, adrenal venous sampling, and/or genetic testing)

### Negative screening tests

- Consider repeating screening tests if the likelihood of primary hyperaldosteronism remains high.
- Consider other causes of secondary hypertension.

## summary

**The effect of drugs on Aldosterone-to-renin ratio (ARR)**

**Drugs with no effect on ARR**

- **Alpha-blockers**
- **Calcium channel blockers**
- **Hydralazine**

**Drugs result in false negative**

- **ACE inhibitors & ARBs >> ↑ renin & ↓ aldosterone**
- **Diuretics >> ↑ both renin & aldosterone**

**Drugs result in false positive**

**Beta-blockers & Methyldopa >> ↓ renin**

## Management:

- Na restriction.
- Bilateral adrenocortical hyperplasia: **aldosterone** antagonist e.g., **spironolactone.**
- Adrenal adenoma: **surgery.**

## Bilateral hyperplasia vs adrenal adenoma:

| bilateral hyperplasia | adrenal adenoma |
|---|---|
| idiopathic adrenal hyperplasia (IAH) | Aldosterone-producing adenomas (APAs) |
| Commonest | common |
| higher prevalence in African Americans, persons of African origin, and, potentially, other blacks. | have more severe hypertension, hypokalemia, and higher urinary aldosterone than IAH. |
| 4 times more prevalent in men than in women | more common in women than in men, with a female-to-male ratio of 2:1. |
| peaking in the sixth decade of life | The typical patient with an APA is a woman aged 30-50 years. |
| renin-angiotensin system (RAS)–mediated **increase** in aldosterone level occurs **with upright posture.** | **decrease** in the aldosterone level **with upright posture** |
| Loss of normal circadian rhythm of aldosterone secretion (normally: lowest around midnight, and highest in early morning) | preserved of normal circadian rhythm of aldosterone secretion |

**aldosterone-producing adrenal adenomas are commoner in young women, whereas bilateral adrenal hyperplasia tends to occur later and is commoner in men.**

## Aldosterone receptor antagonists

**Agents:** spironolactone, eplerenone

### Action

- acts on the distal renal tubules as a competitive antagonist of aldosterone increasing sodium and water excretion and reducing potassium excretion (acts as a potassium-sparing diuretic)
- >> K+ enters cells in exchange for H+ >> amplifies acidosis
- onset of action: requiring 2 or 3 days for maximum effect

### Indications

- Hypertension (especially if hypokalemia is also present)
- Ascites/oedema due to congestive heart failure, nephrotic syndrome, or cirrhosis of the liver (mainly spironolactone)
- Hyperaldosteronism (PCOS)
- Nephrogenic diabetes insipidus (amiloride)
- Hypokalemia
- Hyperandrogenic states, e.g., polycystic ovary syndrome (spironolactone)

### Adverse effects

#### General side effects

- Metabolic and electrolyte imbalances, such as **hyperkalemia** (most common), **hyponatremia,** and **metabolic acidosis,** can lead to cardiac arrhythmias
- Gastrointestinal disturbances (nausea, vomiting, diarrhea)

**Spironolactone-specific side effects**: endocrine disturbances

- **Men:** antiandrogenic effects (e.g., gynecomastia, erectile dysfunction)
- **Women:** amenorrhea

# Cushing's syndrome

It should be noted that exogenous causes of Cushing's syndrome (e.g., glucocorticoid therapy) are far more common than endogenous ones.
causes

**1) ACTH dependent causes:**

- **Cushing's disease (80%): pituitary tumour secreting ACTH producing adrenal hyperplasia.**
- **Ectopic ACTH production** (5-10%): e.g. **small cell lung cancer (SCLC).**

**Cushing's disease (pituitary tumour)** is the most common, non-iatrogenic, cause of Cushing's syndrome.

## Treatment

**1) Trans-sphenoidal** hypophysectomy/adenectomy: the **initial** treatment of choice.
**2) Laparoscopic adrenalectomy:** advised where pituitary surgery has failed.
**3) Ketoconazole** may be an effective treatment for patients **unfit for surgery and preoperatively**, it acts on several of P450 enzymes, including the first step in cortisol synthesis, cholesterol-side chain cleavage, and conversion of 11-deoxycortisol to cortisol. A **daily dose of 600-800 mg** often decrease cortisol production significantly and will help in controlling BP and blood sugar before moving to pituitary surgery.
The recurrence rate for Cushing's disease after surgery is of the order of 20-30% in most series and depends on the size of the tumour with macroadenomas having a higher rate of relapse.
**4) Metyrapone** inhibits 11-beta hydroxylase and as such **inhibits cortisol production**. It has a **relatively rapid onset of action** and as such may be of value **pre-operatively** in improving blood pressure and glycaemic control in patient with pituitary-dependent Cushing's without associated weight gain of other options such as insulin.

**Ectopic ACTH secretion** (e.g. secondary to **small cell lung cancer (SCLC)** which accounts for **50-75% of case of ectopic ACTH)** is **characteristically** associated with **very low potassium levels.**

**1) ACTH independent causes:**

- **Iatrogenic: steroids**
- **Adrenal adenoma** (5-10%)
- **Adrenal carcinoma** (rare)
- Carney complex: syndrome including **cardiac myxoma.**
- Micronodular adrenal dysplasia (very rare)

### 2) Pseudo-Cushing's:

- Mimics Cushing's
- Often due to **alcohol** excess or severe depression
- Causes **false positive** overnight dexamethasone suppression test or **false high** 24 hr. urinary free cortisol with **increased** 9 am and 12 am plasma cortisol.
- **Insulin stress test** may be used to differentiate.
- The mechanism of hormonal abnormality may be due to increased CRH secretion or impaired hepatic metabolism of cortisol.
- Hormonal abnormalities disappear rapidly during abstinence from alcohol.

**NB: Nelson's syndrome** occurs in approximately **30%** of patients **adrenalectomised** for Cushing's disease.
It is probably due to the clinical progression of the pre-existing pituitary adenoma after the restraint of hypercortisolism on ACTH secretion is removed.
Plasma **ACTH** levels are **markedly elevated**.
**Pituitary MRI** defines the extent of the tumour.

## Investigations:

- General findings consistent with Cushing's syndrome
- **A hypokalaemic metabolic alkalosis** may be seen, along with impaired glucose tolerance.
- Ectopic ACTH secretion (e.g. secondary to small cell lung cancer) is characteristically associated with very low potassium levels).

### 1) Confirm high cortisol level:

Do 24 hrs. urinary free cortisol or salivary cortisol level.

### 2) Exclude pseudo-Cushing AND confirm cushing (happening in obesity, alcohol, depression, infection and pregnancy):

## Tests to confirm Cushing's syndrome

**The two most commonly used tests are:**

- **overnight dexamethasone suppression test**
  - this is the most sensitive test and is now used first-line to test for Cushing's syndrome
  - patients with Cushing's syndrome do not have their morning cortisol spike suppressed.

## Localisation tests

**The first-line localisation is 9am and midnight plasma ACTH (and cortisol) levels. If ACTH is suppressed then a non-ACTH dependent cause is likely such as an adrenal adenoma**

## High-dose dexamethasone suppression test

The high-dose dexamethasone suppression test may be used to localise the pathology resulting in Cushing's syndrome.
This test may be interpreted as follows:

| Cortisol | ACTH | Interpretation |
|---|---|---|
| Not suppressed | Suppressed | **Cushing's syndrome due to other causes (e.g. adrenal adenomas)** |
| Suppressed | Suppressed | **Cushing's disease (i.e. pituitary adenoma → ACTH secretion)** |
| Not suppressed | Not suppressed | **Ectopic ACTH syndrome** |

## Other tests

CRH stimulation

- if pituitary source then cortisol rises
- if ectopic/adrenal then no change in cortisol

An insulin stress test is used to differentiate between true Cushing's and pseudo-Cushing's.

## Inferior Petrosal sinus sampling of ACTH:

it is s an **extremely sensitive**, **specific** and **accurate** test for **differentiate** between **pituitary** and **ectopic ACTH** secretion.
It samples venous blood draining from the pituitary gland, using a **femoral approach**. A raised ACTH from here compared to the periphery suggests a pituitary cause.

**The following table summarizes the characteristics of the 3 sources of Cushing disease.**

| | Pituitary Tumor | Ectopic ACTH Production | Adrenal Adenoma |
|---|---|---|---|
| **ACTH** | High | High | Low |
| **High-dose dexamethasone** | Suppression | No suppression | No suppression |
| **Specific test** | MRI, Petrosal vein sampling | Scan chest and abdomen | Scan adrenals |
| **Treatment** | Removal | | |

**Which techniques is the best in differentiating between ectopic Cushing's syndrome and pituitary dependent Cushing's disease?**
**>> Inferior petrosal sinus sampling**
The high-dose dexamethasone suppression test can differentiate between the two forms of Cushing's syndrome, but is not as accurate as inferior petrosal sinus sampling.

**Which feature would favour benign adrenal adenoma as the cause of Cushing's syndrome over the other causes?**
**>> Absence of hirsutism and virilisation** (adrenal adenoma produces cortisol but not the androgens)

## Treatment

### Fit for surgery

- Pituitary adenoma >>Trans-sphenoidal hypophysectomy / adenomectomy is the initial treatment of choice.
- Adrenocortical tumor: laparoscopic or open adrenalectomy
- Laparoscopic adrenalectomy would be advised where pituitary surgery has failed.
- The recurrence rate for Cushing's disease after surgery is 20-30% and depends on the size of the tumour with macroadenomas having a higher rate of relapse.
- ACTH-secreting ectopic tumor: resection of the ectopic foci (e.g., bronchial carcinoid)

### Unfit for surgery

- **Ketoconazole may be an effective treatment for patients unfit for surgery**
- **Mitotane** is an adrenolytic drug licensed for symptomatic treatment of advanced or inoperable adrenocortical carcinoma >> **improve the prognosis**

**What is the optimum time for the administration of hydrocortisone to a patient undergoing bilateral adrenalectomy for Cushing's disease?**
**>> Immediately following the removal of both adrenal glands.**

**Perioperative management of a cortisol producing adenoma includes:**
**Peri and postoperative hydrocortisone with further assessment of postoperative cortisol secretion**

**May 2008 exam: A 62-year-old man is investigated for hypertension and proximal myopathy. On examination he is noted to have abdominal striae. Which one of the following is most associated with ectopic ACTH secretion?**
**>> Small cell lung cancer**

# Addison's disease (primary hypoadrenalism)

**Autoimmune destruction** of the adrenal glands (**Autoimmune adrenalitis**) is the commonest cause of hypoadrenalism in the UK, accounting for **80%** of cases.

**21 Hydroxylase** is the enzyme involved in the cholesterol steroid pathway and has been found to be present in approximately 80% of cases.

**Anti-21 hydroxylase antibody** is typically found in auto-immune adrenalitis (Addison's disease).

**Addison's disease** (autoimmune hypoadrenalism) is associated with other endocrine deficiencies in approximately 10% of patients.

Hyponatraemia and a high potassium in a patient with lethargy is highly suggestive of Addison's disease. >>> Steroids should be given as soon as possible.

## Features

- Lethargy, weakness, anorexia, nausea & vomiting, weight loss.
- **Hyperpigmentation** (especially **palmar creases**), vitiligo, **loss of pubic hair in women (due to DHEA deficiency).**
- **Crisis: collapse, shock, pyrexia.**
- **Hypo-tension, hypo-glycaemia, hypo-natremia.**
- **Hyper-kalemia.**
- **Hyper-Renin and Hypo-Aldosterone.**
- **Metabolic acidosis. (Hypo PH)**
- **Macrocytic (pernicious) anaemia may occur**
- **Blood: Eosinophilia, lymphocytosis & Neutropenia.**
- **Slight elevation of TSH.**
- **Mild hypercalcaemia.**

**Addison's disease:**
**5 Hypo:**
1) Hypo-tension
2) Hypo-glycaemia
3) Hypo-natremia
4) Hypo-PH (MA)
5) Hypo-aldosterone

**2 Hyper:**
1) Hyper-**kalemia**
2) Hyper-**renin**

The **most common** cause of adrenal insufficiency is **autoimmune adrenalitis.**

## Other causes of hypoadrenalism:

**1) Primary causes:**

- **Tuberculosis.**
- **Metastases** (from e.g. **bronchial, breast, kidney**).
- **Antiphospholipid syndrome (Hughes' syndrome).**
- **Meningococcal septicaemia** (Waterhouse-Friderichsen syndrome).

- **HIV:** secondary to **CMV-adrenalitis** which is an immune reconstitution syndrome.
- Severe illness.

2) **Secondary causes:**
   - Pituitary disorders (e.g., tumors, irradiation, and infiltration).
   - Drugs: ACEI, Heparin, Lead poisoning.
3) **Exogenous glucocorticoids therapy.**
4) **Pseudo-hypoaldosteronism:** due to primary aldosterone resistance (rare, but may occur due to spironolactone).

The two causes of Addison's in immunocompromised patient is **HIV (CMV-Adrenalitis)** and **TB.**

## Investigations

1) The definite investigation is **ACTH stimulation test (Short Synacthen test):**
   - Plasma cortisol is measured before and **30 minutes** after giving Synacthen **250ug IM** (Normal response to **increase** cortisol **greater than 550** nmol/L), if below than this so this is inadequate response to synacthen and there is adrenal insufficiency.

**Addison's disease. >>> Short Synacthen test >>>** will show **failure** of **cortisol** secretion to **exceed** 550 nmol/L **after** 30 minutes following IM/SC administration of ACTH.

2) **Adrenal autoantibodies**, are present in **75% of cases**, such as **anti-21-hydroxylase Ab** may also be demonstrated.
3) **If an ACTH stimulation test is not readily available (e.g., in primary care) then sending a 9 am serum cortisol can be useful:**
   - 500 nmol/l makes Addison's very unlikely
   - < 100 nmol/l is definitely abnormal
   - **100-500 nmol/l should prompt a ACTH stimulation test to be performed**

**Treatment:** Exogenous glucocorticoid therapy: **Hydrocortisone 100 mg IV TDS.**

**NB:** Usually TFTs are abnormal at the time of diagnosis of adrenal insufficiency (↑TSH and ↓T4)
**EX:** In diabetic patient with autoimmune **hypoadrenalism** plus **hypothyroidism**, you cannot commence thyroid hormone replacement at this stage as it may precipitates a rapid deterioration in his adrenal crisis.

It would be most important to **confirm the diagnosis** of adrenal insufficiency by short synacthen test, then commence **IV hydrocortisone** then **re-check the TFTs a few weeks later** after stabilising glucocorticoid replacement.

**EX**: Old patient with **severe hypoglycaemia** and **witnessed seizures** at ER. He is given **50 ml of 50% dextrose** and he slowly recovers over the next one hour. **A serum cortisol concentration later returns as 800 nmol/L (120-600).** >>> It is **Insulinoma** >>> to be confirmed by Prolonged 72 hour fast.
**The appropriate cortisol response during his hypoglycaemic episode (cortisol 800) excludes hypoadrenalism.**

**N.B: Dehydroepiandrosterone (DHEA)** is the most abundant circulating adrenal steroid. Adrenal glands are the main source of DHEA in females - loss of functioning adrenal tissue as in Addison's disease may result in **symptoms secondary to androgen deficiency**, such as **loss of libido and slight loss of pubic hair**. Research is ongoing as to whether routine replacement of DHEA is beneficial.

The **pigmentation**, which is due to **increased** adrenocorticotropic hormone (**↑ACTH**) in hypoadrenalism, would **exclude pituitary** infarction as the cause of the hypoadrenalism.

**EX**: Female Pt. with history of **recurrent DVT** and **confirmed hypoadrenalism (↓NA, ↑K, +ve short Synacthen test)** >>> **Antiphospholipid syndrome.**
APL syndrome is associated with arterial and venous thrombosis and has a predilection for **the adrenal veins** causing **adrenal infarction / Hge** with consequent **hypoadrenalism.**

**WaterhOuse-Frederickson syndrome**
adrenal failure due to bleeding into the adrenal glands (otherwise referred to as haemorrhagic adrenalitis) and is most commonly caused by meningococcal septicaemia.

A person with Addisons' who vomits should take **IM hydrocortisone** until

**Wolman's syndrome** is characterised by:
- primary adrenal failure,
- hepatosplenomegaly, and
- steatorrhoea.

**exam**: Addison's disease C/O a decrease in her libido. On examination there is a slight loss of pubic hair. What is the most likely cause? **>> Dehydroepiandrosterone (DHEA) deficiency**

# Addisonian crisis

## Causes

- sepsis or surgery causing an acute exacerbation of chronic insufficiency (Addison's, Hypopituitarism)
- adrenal haemorrhage eg Waterhouse-Friderichsen syndrome (fulminant meningococcemia)
- steroid withdrawal

## Signs and symptoms

### Neurological

- syncope
- confusion
- lethargy
- convulsions

### Haemodynamic

- hypotension
- hypothermia

### Biochemical

- hyponatraemia
- hyperkalaemia
- hypoglycaemia

## Management

- hydrocortisone 100 mg im or iv
- 1 litre normal saline infused over 30-60 mins or with dextrose if hypoglycaemic
- continue hydrocortisone 6 hourly until the patient is stable. No fludrocortisone is required because high cortisol exerts weak mineralocorticoid action
- oral replacement may begin after 24 hours and be reduced to maintenance over 3-4 days

# Secondary and tertiary hypoadrenalism

**Definition:** Adrenal hypofunction due to a lack of adrenocorticotropic hormone (ACTH)

## Pathophysiology

- ↓ ACTH >> hypoandrogenism and hypocortisolism
- **Aldosterone synthesis is not affected** (mineralocorticoid production is controlled by RAAS and angiotensin II, not by ACTH).
- If ↓ ACTH induced by ↓ CRH, then it is called tertiary adrenal insufficiency (↓ CRH >> ↓ ACTH).

## Causes

**Hypopituitarism:** ↓ ACTH >> ↓ endogenous cortisol

- Pituitary tumors
- Craniopharyngioma (in youngers)
- Irradiation

**Conditions that decrease CRH production (tertiary adrenal insufficiency):** ↓ CRH >> ↓ ACTH >> ↓ cortisol release

- The most common cause is sudden discontinuation of chronic glucocorticoid therapy (e.g., infection, trauma, surgery) during prolonged glucocorticoid therapy
- Rarer causes include hypothalamic dysfunction (e.g., due to trauma, mass, haemorrhage, or anorexia).

> Secondary and tertiary adrenal insufficiency are far more common than primary adrenal insufficiency

## Feature

Symptoms and signs are similar to those of Addison disease

**Differentiating features include:**

- **Absence of hyperpigmentation** because ACTH secretion is not increased.
- **Absence of mineralocorticoid deficiency** (Aldosterone synthesis is not affected)
  - No dehydration or hypotension
  - Relatively normal electrolyte. Hyponatremia if it occurs, is due to increased vasopressin secretion >> volume expansion >> dilutional hyponatremia. Hyperkalemia is not present
- **Associated features of underlying cause,** e.g., visual field defects if pituitary tumour.

- **Other endocrine deficiencies** may manifest due to panhypopituitarism (↓thyroid and gonadal function and hypoglycemia). Adrenal crisis is likely if a patient is treated with thyroxine, without hydrocortisone replacement.
- **Hypoglycemia is more common** in secondary adrenal insufficiency.

**Primary adrenal insufficiency >> Pigments the skin.**
**Secondary adrenal insufficiency >> Spares the skin.**
**Tertiary adrenal insufficiency is due to >> Treatment (cortisol).**

## Diagnosis

| Confirmatory Serum Testing for Secondary Adrenal Insufficiency | |
|---|---|
| **Test** | **Result** |
| ACTH | Low(< 5 pg/ml) |
| Cortisol | Low (< 5 µg/dl [138 nmol/L)) |
| ACTH stimulation test (short Synacthen test) | Normal or subnormal |
| Prolonged (24-h) ACTH stimulation test (Long Synacthen test) | Cortisol should continue to rise for 24 h |

## Advanced level

**Long Synacthen test** (prolonged ACTH stimulation test for 24 h)

- **Aim:**
  - To diagnose secondary (or tertiary, ie, hypothalamic) adrenal insufficiency.
- **Before the test:**
  - **The simple short test is usually done initially,** because a **normal** response obviates the need for further investigation.
  - If short Synacthen test is subnormal (failure to respond to ACTH >>↓ cortisol) **and** secondary adrenal insufficiency is suspected >> do long Synacthen test
  - **Because pituitary failure may cause adrenal atrophy and hence failure to respond to ACTH,** the patient may need to be primed with **long-acting ACTH 1 mg IM once/day for 3 days** before the ACTH stimulation test if pituitary disease is suspected.
- **Method:**
  - Cosyntropin 1 mg IM is given, and cortisol is measured at intervals for 24 h, typically at 1, 6, 12, and 24 h.

- **Interpretation:**
  - In primary adrenal failure: No significant cortisol rise.
  - In secondary adrenal failure: **gradually rises cortisol to a peak at 24 hours**
  - Prolonged stimulation of the adrenal glands by ACTH in the long Synacthen test >> **gradually rises cortisol to a peak at 24 hours** >> confirm the diagnosis of secondary adrenal failure.
  - in some cases of long-standing adrenal atrophy due to secondary adrenal insufficiency, the adrenal glands will not respond even after 24 hours and will require several daily doses of depot Synacthen before an adrenal response is seen.

**CT or MRI of the brain to rule out a pituitary tumor or pituitary atrophy.**

## Nelson's syndrome

### Aetiology

- bilateral adrenalectomy in patients with a previously undiscovered pituitary adenoma
- occurs in 30% of **patients adrenalectomised for Cushing's disease.**

**Pathophysiology:** Bilateral adrenalectomy >> no endogenous cortisol production >> no negative feedback from cortisol on hypothalamus >> increased CRH production >> uncontrolled enlargement of preexisting ACTH-secreting pituitary adenoma >> increased secretion of ACTH and melanocyte-stimulating hormones (MSH) >> symptoms of pituitary adenoma and t MSH.

### Features

- Headaches, bitemporal hemianopia (mass effect)
- Cutaneous **hyperpigmentation:** arises from the MSH products of the proteolysis of POMC, which also produces ACTH.

### Diagnosis

- **High levels of beta-MSH and ACTH**
- Pituitary adenoma on MRI confirms the diagnosis.

**Treatment:** Surgery (e.g., transsphenoidal resection) and/or pituitary radiation therapy (e.g, in the case of tumor residues after surgery)

### Monitoring

- ACTH levels
- serial pituitary imaging.

# Phaeochromocytoma

## Basics:

- Phaeochromocytoma is a **rare** catecholamine secreting neuroendocrine tumour of the medulla of the adrenal glands (**originating in the chromaffin cells**), or extra adrenal chromaffin cells.
- It secretes excessive amounts of **catecholamines**, usually **adrenaline** if in the adrenal gland (not extra adrenal) and **noradrenaline.**
- About **10% are familial** and may be associated with:
  - **MEN type II a and b,**
  - **Neurofibromatosis** and
  - **Von Hippel-Lindau syndrome.**
- **Bilateral in 10%**
- **Malignant in 10%**
- **Extra-adrenal in 10%**: sometimes called **paragangliomas** (most common site = organ of Zuckerkandl, adjacent to the bifurcation of the aorta)

Adrenal glands are the only source of adrenaline in the body

**Pheochromocytoma >>>> rule of 10 (10% BM EF)** (Bilateral, Malignant, Extra-adrenal, Familial)

## Features (symptoms & Signs):

- ↑ HR
- ↑ BP, including paroxysmal (sporadic, episodic) increase of BP which sometimes can be more difficult to detect.
- **Orthostatic hypotension** (↓ SBP ≥ 20 mmHg or ↓ DBP ≥ 10 mmHg on making the patient stand)
- Skin: hot flushes and ? pigmentation
- Diaphoresis
- Flank abdominal pain, vomitting
- Restless and anxiety often resembling that of a panic attack
- Localized amyloid deposits found microscopically.
- **Episodic paroxysmal headache was present in 80%. It was usually of rapid onset**, bilateral, severe, and throbbing (vascular), and associated with nausea in about half of the cases.
- **Glycosuria** occurs **during** the attack in **30%** of cases.
- **Goiter if MEN 2.**

**EX:** A **young man** presented with **intermittent severe headaches** with **high BP** (190/110 mmHg) and **high HR** (112 bpm) with ↓ **Na** and ↓**K** >>> **phaeochromocytoma** >>> **24 hour urinary collection of catecholamines.**

**EX:** A young male with a 3 months history of episodes of HTN, headache, dizziness, vague central abdominal discomfort, goiter and glycosuria >>> **Pheochromocytoma (MEN 2).**

**NB:** Pheochromocytoma can also present with **severe hypotension** from **catecholamine-induced cardiomyopathy.**
**EX:** Female pt. 50 years old severely unwell at ER with 3-h history of **severe SOB, tachycardia, hypotension** BP 80/60 mmHg, **bilateral fine basal rales** up to mid lung zones, ECHO: severe **cardiomyopathy** with **EF 30%,** pt. admits to have **recurrent episodes of headache** over the past month, **CT abdomen** shows **intra-abdominal mass 5 cm** close to the origin of inferior mesenteric artery.
This is **Pheochromocytoma (extra-adrenal)** with **catecholamine-induced cardiomyopathy**

## Investigations

- **Plasma free metanephrines test(expensive)**
  - **The best initial test**
  - **The most sensitive test**
- **24 hr urinary collection of metanephrines**

The 24 hrs urinary collection of **metanephrines** is preferred to that of vanillylmandelic acid as it has a **higher sensitivity.** Three 24 hrs collections are needed as some patients **have intermittently raised levels.**

  - **The most specific test** (sensitivity 86%)
  - **False positive urinary metanephrines** can occur as a result of:
    - hypoglycaemia, **stress,** exercise, drugs such as methyldopa, dopamine agonists or ganglion-blocking antihypertensives, various foodstuffs including coffee, chocolate, bananas and citrus fruits.

**N.B:**

- The presence of **noradrenaline alone** usually indicates an **extra-adrenal tumour.**
- **Small** adrenal tumours tend to produce more **adrenaline** whereas **larger** adrenal tumours produce more **noradrenaline**
- **Tricyclic antidepressants** and **labetalol** interfere with adrenaline measurements and should be **stopped for 4 days**

- **Genetic testing:** if MEN2A, MEN2B, NF1, or VHL is suspected

- **Adrenal/abdominal CT or MRI** (after positive biochemistry tests to localize tumor)
  - The definitive **methods for localisation**
  - **MRI: unlike most other adrenal tumours, demonstrates a distinctive 'bright white' signal on T2-weighted MRI..**
- **18F fluorodopamine PET scanning is** superior to MIBG in localizirnig **metastatic disease.**

## Treatment:

- **Surgery** is the definitive management.
- The patient must first be stabilized with medical management:
  - **Alpha-blocker** (e.g. phenoxybenzamine), **given before a**
  - **Beta-blocker** (e.g. propranolol)

**PH**aeochromocytoma >>> give **PH**enoxybenzamine before beta-blockers
Unopposed beta blockade should not be used in the management of phaeochromocytoma because of the risk of paradoxical increases in BP.

**Phenoxybenzamine:**
- It is the most potent available alpha blocker and is the treatment of choice for pheochromocytoma. **Starting dose 10 mg BID up to maximum 20 mg QDS.**
- **Beta blockade** can be started around **3 days after** phenoxybenzamine.

**IV** phenoxybenzamine is commonly used for the 3 days prior to surgery to ensure complete alpha blockade.

**Management of phaeochromocytoma in pregnancy** is difficult with maternal and fetal mortality both approximately 50%.
The primary management goal is to prevent hypertensive crisis, which can be harmful to both mother and foetus.
**Alpha blockade** (phenoxybenzamine or Doxazosin) should be started as soon as the diagnosis is made, and should be given **for 10-14 days.**
**Surgery** is the **definitive** treatment for phaeochromocytoma. The timing remains challenging and controversial.
**Laparoscopic adrenalectomy** is indicated if tumour mass is **less than 7 cm.**
Vaginal delivery carries a higher mortality rate of 31%, compared to 19% with **C-section. General anaesthesia is recommended.**
The correct management in this situation is therefore to **initiate alpha-blockade** and **arrange delivery by C-section with GA.**

**Phaeochromocytoma in pregnancy >>> alpha-blocker + arrange delivery by C-section by GA + later surgery for the tumour.**

**NB:** Usually **medullary carcinoma of the thyroid (elevated serum calcitonin)** is associated with pheochromocytoma, so adrenal gland imaging is recommended in any patient with medullary carcinoma of the thyroid.
**NB**: DD of **FUO (Fever of unknown origin)** and **bilateral adrenal swelling** is: **TB, Lymphoma** or **Histoplasmosis.**

# Congenital adrenal hyperplasias (CAH)

CAH due to 11-beta hydroxylase deficiency can cause apparent mineralocorticoid excess syndrome (AMES) resulting in hypertension and hypokalemia

**Which of the following is the best investigation to monitor a patient with classic salt wasting Congenital adrenal hypreplasia (CAH)? 17 hydroxyproesterone (17 OHP) levels.**

## Overview

- group of autosomal recessive disorders
- affect adrenal steroid biosynthesis
- in response to resultant low cortisol levels the anterior pituitary secretes high levels of ACTH
- ACTH stimulates the production of adrenal androgens that may virilize a female infant.

This results in **cortisol deficiency**, **aldosterone deficiency** and **androgen excess.**

## Causes

- **21-hydroxylase deficiency (90%)**
- 11-beta hydroxylase deficiency (5%)
- 17-hydroxylase deficiency (very rare)

| Type | 21 β - hydroxylase deficiency | 11 β - hydroxylase deficiency | 17α- hydroxylase deficiency |
|---|---|---|---|
| **Blood pressure** | **Hypotension** | Hypertension | Hypertension |
| **Acid-base disorders** | **Metabolic acidosis** | Metabolic alkalosis | Metabolic alkalosis |
| 17-Hydroxyprogesterone | Elevated | Elevated | **Decreased** |
| 11-Deoxycorticosterone | **Decreased** | Elevated | Elevated |
| Corticosterone | Decreased | Decreased | **Elevated** |
| Potassium | **Elevated** | Decreased | Decreased |

- . All 3 types of CAH cause >> ↓ cortisol + ↑ ACTH
- 11-deoxycorticosterone **decreased only** in the 21-hydroxylase deficiency (increased in other 2 types)
- **Testosterone decreased only** in the 17-hydroxylase deficiency (increased in other 2 types)

A female born with virilisation but has **elevated blood pressure** likely has a deficiency in **11 beta-hydroxylase.**

- **ACTH excess >> hyperpigmentation (common feature in all forms of CAH)**
- **Under- and over-treatment of CAH >> Premature epiphyseal closure >> short stature**
- **Patients might complain of no other symptoms apart from primary amenorrhoea.**
- **The clinical presentation may be indistinguishable from polycystic ovarian syndrome, with hirsutism being a dominant feature.**

## Treatment:

- If the main concern is infertility, **ovulation induction** is the treatment of choice.
- **If hirsutism is the presenting problem then anti-androgens (such as flutamide 250 mg cap) should be used** to treat hirsutism, but glucocorticoids are generally **not** required.
- The treatment of CAH is **the lowest dose of glucocorticoid (Hydrocortisone)** that suppresses (not totally) adrenal androgens, whilst maintaining normal growth and weight gain.

**NB: Hydrocortisone** has a relatively **short half-life** and must therefore be administered **twice daily** whilst the **preferred** mode of glucocorticoid replacement in **children** is hydrocortisone **as it minimises growth suppression.**
**NB: Efficacy** of treatment of CAH is best **monitored** by **17-OH progesterone** and **androstenedione** levels.

**EX:** An 18-year-old woman comes to the clinic complaining of acne and hirsutism, secondary amenorrhoea. She has no medical history of note and her only medication is the oral contraceptive pill. Lab: **hypogonadotrophic hypogonadism** (↓Estrodoil, ↓FSH, ↓LH) >>> **CAH** The **non-classical "mild"** form with elevated level of ↑ **17-OH progesterone**

**EX: Young female** with **hirsutism** >>> check (5):
- FSH, LH, oestradiol
- Testosterone
- Androstenedione
- Dehydroepiandrosterone sulphate (DHEAS)
- 17-hydroxyprogesterone

# Gonadal disorders

## Disorders of sex development

The table below lists the most common disorders of sex development:

| Name | Karyotype | Notes |
|---|---|---|
| Androgen insensitivity syndrome | 46 XY | X-linked recessive condition. Defect in androgen receptor results in end-organ resistance to testosterone causing genotypically male children (46XY) to have a female phenotype. Rudimentary vagina and testes present but no uterus. Testosterone, oestrogen and LH levels are elevated |
| 5-α reductase deficiency | 46 XY | Autosomal recessive condition. Results in the inability of males to convert testosterone to dihydrotestosterone (DHT). Individuals have ambiguous genitalia in the newborn period. Hypospadias is common. Virilization at puberty. |
| Male pseudohermaphroditism | 46 XY | Individual has testes but external genitalia are female or ambiguous. may be secondary to androgen insensitivity syndrome |
| Female pseudohermaphroditism | 46 XX | Individual has ovaries but external genitalia are male (virilized) or ambiguous. May be secondary to congenital adrenal hyperplasia |
| True hermaphroditism | 46 XX or 47 XXY | Very rare, both ovarian and testicular tissue are present |

# Disorders of sex hormones

The table below summarises the findings in patients who have disorders of sex hormones:

| Disorder | LH | Testosterone |
|---|---|---|
| Primary hypogonadism (Klinefelter's syndrome) | High | Low |
| Hypogonadotrophic hypogonadism (Kallman's syndrome) | Low | Low |
| Androgen insensitivity syndrome | High | Normal/high |
| Testosterone-secreting tumour | Low | High |

# Dihydrotestosterone (DHT)

**Composition:** Testosterone is a steroid hormone and can be converted to oestradiol.

**Production:** **LH** stimulates testosterone production and **FSH** spermatogenesis

**Binding:** It binds to intracellular receptors and is mostly bound to sex-hormone binding globulin (SHBG)

## Conversion

- Testosterone converted to dihydrotestosterone **(DHT)** in the body by the enzyme **5a- reductase**. DHT is a more active compound than testosterone.
- The absence of **5a-reductase** or the absence of **DHT receptors** leads to testicular feminisation.

## Function

- During fetal development and early life: differentiation of the penis, scrotum, **and** prostate.
- expression of male secondary sex characteristics
- During late adulthood: prostate growth, male pattern baldness, **and** sebaceous gland activity.

## Deficiency

↓ testosterone is due to either:

- ↓ free level due to ↓ production (Leydig and pituitary dysfunction) (Lead to ↑ synthesis of SHBG)
  - increasing age: total testosterone concentrations fall slightly, and free testosterone fall more.

- ↓ activity at receptor often due to androgen receptor deficiency (5a-reductase deficiency).
- Patients with **Sa-reductase deficiency** will have ambiguous genitalia at birth until they reach puberty, when the testosterone surge causes growth of external male genitalia, however, these patients are otherwise healthy. **Individuals** with this deficiency sometimes change their **gender** role in adolescence.
  - **obesity** (hyperinsulinaemia of obesity >>↓ SHBG levels >> ↓ testosterone (/ow ***SHBG*** and ***normal free testosterone)***

## Evaluation

- Initial evaluation: serum testosterone in the early morning, fasting.
- Testosterone levels vary according to the **degree of binding to albumin and SHBG;** (↑ SHBG >> ↑ total testosterone - when testosterone production is low-).
- The **equilibrium dialysis method** is most useful for measurement of **free testosterone** (not bound to protein)
- If the testosterone is low:
  - measurement of **LH** and **FSH** to determine if the hypogonadism is primary or secondary. **If secondary >> assessment of other pituitary hormones.**
  - If the patient has **multiple** pituitary hormonal deficiencies and/or if the testosterone **is less** than 200 ng/dl, wesuggest MRI of the sella.

## Testosterone therapy

### Indications

- hypogonadal men to induce and maintain secondary sex characteristics and correct symptoms of testosterone deficiency.
- Older men (>65 years) with age-related decline in testosterone concentration:
  - routinely prescribing testosterone therapy is not recommended
  - **In symptomatic** (such as low libido or unexplained anemia) and **consistently and** unequivocally low morning testosterone, testosterone therapy **may** be offered on an individualized basis after **discussion** of the potential risks and benefits.
  - **HIV-infected men with weight loss and low testosterone** (when other causes of weight loss have been excluded) **to** induce **and maintain body weight and lean mass gain.**

**Target**: For patients receiving testosterone enanthate, **the testosterone level should be between 400 and 700 ng/dl at about half-way between administrations** (one week after injection) which are generally given every two weeks.

**Which type of testosterone therapy is most likely to result in an increase in dihydrotestosterone level?**

- Dihydrotestosteone levels increase with the use of a testosterone **scrotal patch** due to the high concentration of **5a-reductase in genital skin.** Levels may return to normal after discontinuation; however, they often remain elevated.

**Benefits of testosterone treatment**

- ↑ sexual interest and activity, slight improvement in walking, slight improvement in mood, ↑ hemoglobin, and ↑ bone mineral density (BMD).
- No change in energy or cognition is expected.

**Side effects**

- Erythrocytosis leading to **elevated haematocrit**
  - Haematocrit should be measured 3-6 months after initiating therapy and yearly thereafter.
  - Guidelines suggest that if haematocrit is increased and no other underlying cause is found, the dose should be down-titrated.
- PSA
  - Androgen replacement therapy is contraindicated in patients with prostate cancer and breast cancer.
  - **Urological consultation is recommended** if:
    - ↑ PSA > 1.4 ng/ml within a 12-month period,
    - a PSA velocity > 0.4 ng/ml/year using the level after 6 months of testosterone therapy as the reference
    - abnormality on digital rectal examination, or
    - an I-PSS score of greater than 19.

## Selective Estrogen Receptor Modulators (SERMs)

### Raloxifene

**Mechanism of action**

- estrogen **antagonist** in **breast** and **endometrium**
- **agonist** in bone to increase mineralisation

**Clinical use**

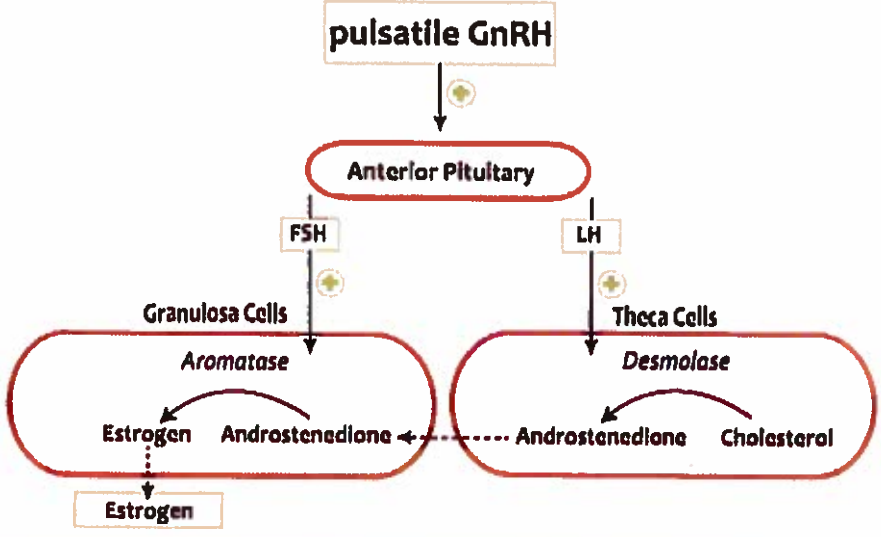
- osteoporosis in menopausal women
- breast cancer prevention in women high risk for breast cancer

### Toxicity

- ↑ risk of venous thromboembolism
- induces menopause >> hot flashes

## Physiological effects of LH, FSH, and sex hormones

- ♀: **Ovaries**
  - **FSH:** follicular maturation → ↑ **estrogen**
  - **LH:** ↑ estrogen, **ovulation**, and ↑ **progesterone**
- ♂: **Testicles**
  - **FSH:** production of sperm, ↑ **inhibin**
  - **LH:** stimulation of Leydig cells → ↑ **production of testosterone**




## Klinefelter's syndrome

Klinefelter's syndrome is associated with karyotype 47, XXY

### Features

- often taller than average
- lack of secondary sexual characteristics
- small, firm testes
- infertile
- gynaecomastia - increased incidence of breast cancer
- elevated gonadotrophin levels

**Diagnosis** is by chromosomal analysis

## Kallmann's syndrome

Kallman's syndrome is a recognised cause of delayed puberty secondary to hypogonadotrophic hypogonadism. It is usually inherited as an X-linked recessive trait. Kallman's syndrome is thought to be caused by failure of GnRH-secreting neurons to migrate to the hypothalamus.

The clue given in many questions is lack of smell (anosmia) in a boy with delayed puberty

### Features

- 'delayed puberty'
- hypogonadism, cryptorchidism
- anosmia
- sex hormone levels are low
- LH, FSH levels are inappropriately low/normal
- patients are typically of normal or above average height

cleft lip and palate and difficulty in hearing duo sensory- neural loss

## Gynaecomastia

Gynecomastia describes an abnormal amount of breast tissue in males and is usually caused by an **increased oestrogen: androgen ratio**.
It results from an imbalance of oestrogens and androgens in the male patient.

It is important to differentiate the causes of galactorrhoea (due to the actions of prolactin on breast tissue) from those of gynaecomastia.

The incidence of gynaecomastia typically occurs at 3 distinct periods of life:

- **Neonatal** - due to maternal oestrogens crossing the placenta.
- **Puberty** - low testosterone and dihydrotestosterone (DHT) during puberty.
- **Adult life** - typically 50-80-years-old, which may be due to primary testicular failure, obesity or alcohol excess.

### Causes of gynaecomastia:

- Physiological: normal in neonatal, puberty and elderly.
- **Syndromes with androgen deficiency: Kallman's, Klinefelter's**
- Testicular failure: e.g. mumps
- Testicular cancer e.g. **seminoma** secreting **hCG**
- Ectopic tumour secretion
- **Liver cirrhosis** (only 8% of cases)
- **Renal failure: Haemodialysis**

- **Hyperthyroidism** (Gynaecomastia is seen in up to a **third** of **men** with thyrotoxicosis, but is **not a feature of hypothyroidism).**
- **Drugs** related gynaecomastia (it accounts **10-25%** of cases): see below

## Drug causes of gynaecomastia:

- **Spironolactone** (most common drug cause)
- **Cimetidine**, also **omeprazole**
- Digoxin
- **Finasteride**
- Gonadorelin analogues e.g. **Goserelin (Zoladex ®),** buserelin: It is used in the treatment of **advanced prostate cancer.**
- Oestrogens, anabolic steroids
- Cannabis

**Very rare drug causes of gynaecomastia:**

- TCA (e.g. Amitriptyline)
- Isoniazid
- Calcium channel blockers
- Methyldopa
- Busulfan
- Heroin

**N.B:** Tamoxifen may be used to treat gynaecomastia.

**NB:** Neither hyperprolactinaemia nor hypopituitarism disturb this ratio and are rarely associated with gynaecomastia (i.e. prolactinoma not cause gynaecomastia).

**NB: Spironolactone** causes gynaecomastia by several mechanisms:

- It can block androgen production by inhibiting enzymes in the testosterone synthetic pathway, and
- It can also block receptor binding of testosterone and dihydrotestosterone.
- It displaces oestradiol from sex hormone binding globulin (SHBG), which increases free oestrogen levels.

**NB:** The mechanism of digoxin-induced gynaecomastia is thought to be a direct action at oestrogen receptors.

**N.B:**
- Primary hypothyroidism >> ↑ Prolactin
- Hyperthyroidism >> Gynaecomastia

# Hypogonadism

## Primary hypogonadism (Hypergonadotropic hypogonadism)

if LH and FSH are not elevated a primary hypogonadism is excluded.

**Pathophysiology:** gonadal insufficiency → insufficient sex steroid production (↓ testosterone, ↓ estrogen) → increased gonadotropin secretion (↑ FSH and ↑ LH) from the anterior pituitary → ( lack of negative feedback from the impaired gonads)

**Causes**

**Congenital abnormalities:** (Primary gonadal insufficiency)

- Turner syndrome (females)
- Klinefelter syndrome (males)
- androgen insensitivity syndrome

**Acquired diseases:** (Secondary gonadal insufficiency) >> (damage to leydig cells or ovarian tissue)

- Medications (Radiation, chemotherapy, Ketoconazole, Glucocorticoids, Environmental toxins)
- autoimmune disease,
- infections (**mumps**, tuberculosis)
- **Testicular tumour, infiltration**
- Chronic systemic illnesses (eg: Hepatic cirrhosis, Chronic renal failure)
- Ageing **Andropause (↓ testosterone with age >50).**
- primary testicular failure (**idiopathic failure**).

**Investigations**

- (↑ LH & (FSH) + ↓ testosterone + ↓ sperm count
- **Testicular ultrasound (the most important investigation after blood hormones)**

## Secondary hypogonadism (hypogonadotrophic hypogonadism)

In male patients with low libido have been found to have a low testosterone first line investigation should include prolactin and LH to assess for a central cause

**Pathophysiology:** ↓ pituitary gonadotropins (↓ FSH and ↓ LH) → ↓ testosterone and ↓ estrogen

**Causes**

- Genetic disorders (e.g. **Kallmann's syndrome** Prader-Willi syndrome Gaucher's disease)

- Hypothalamic and/or pituitary lesions due to: Neoplasm (e.g. prolactinoma, craniopharyngioma, astrocytoma)
- Malnutrition (e.g., anorexia nervosa)
- Chronic diseases (e.g., inflammatory bowel disease, hypothyroidism, cystic fibrosis, **diabetes** and obesity.)

### Investigations

- serum **testosterone** and **sperm count** are **subnormal + normal or reduced LH and FSH**
- **Prolactin level** (↑Prolactin reduces LH and FSH)
- measure of **free testosterone** (as total testosterone can be low due to SHBG being decreased in obesity and with ageing).
- pituitary MRI the best imaging to exclude other pituitary pathology.

## Clinical features

- **Delayed puberty**
- Developmental abnormalities with genitalia (undescended testes, hypospadias)
- Infertility (↓ sperm count), impotence, and/or ↓ libido
- **Secondary** amenorrhea

## Treatment

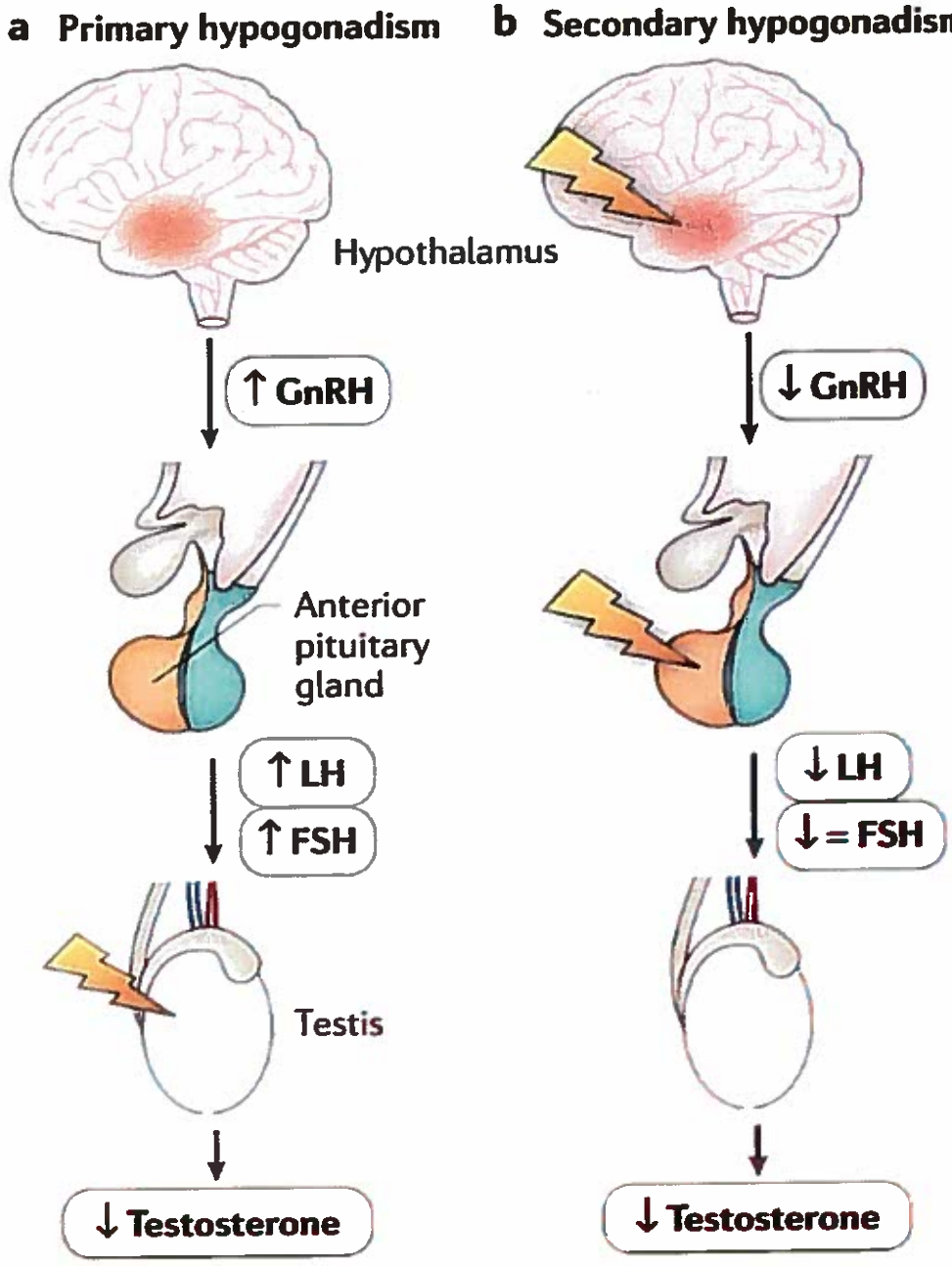
- Treat underlying cause: e.g., surgical excision of tumors, pharmacotherapy for prolactinomas
- Hormone replacement therapy

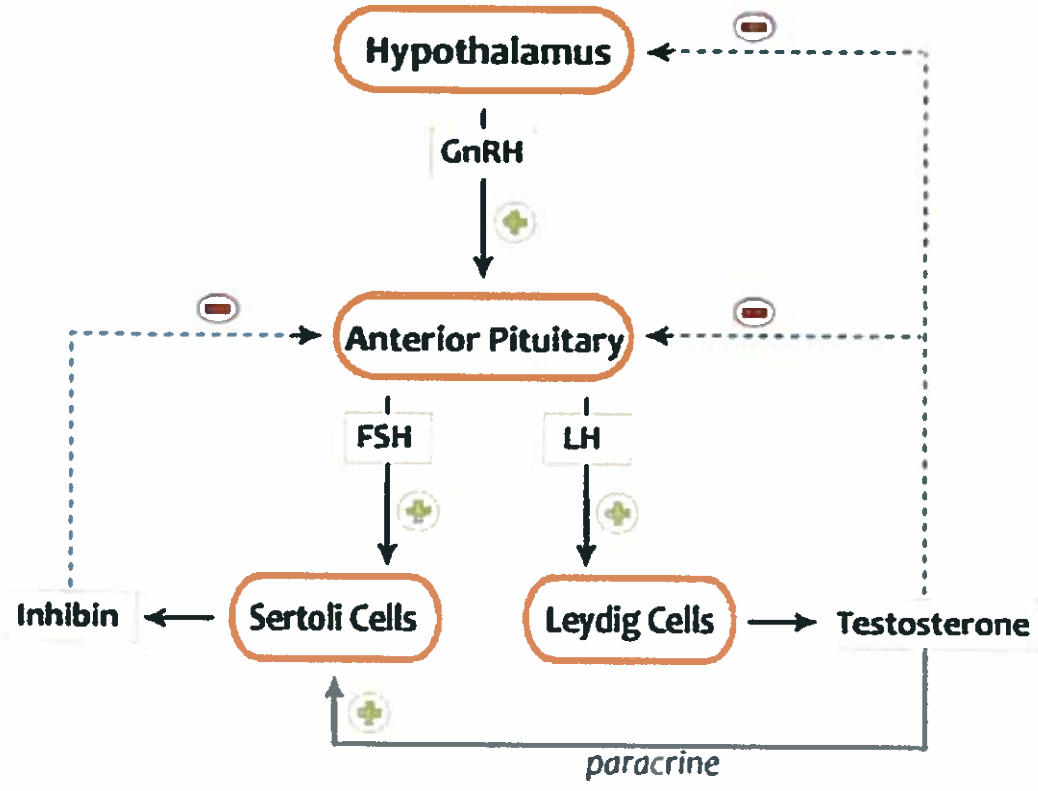
**Poor ability to concentrate is most consistent with post-pubertal loss of testicular function,** whereas (High-pitched voice, Gynecomastia, Disproportionately long arms and legs, Scant pubic and axillary hair) are most consistent with hypogonadism that develops before puberty.

**Tip to remember**

Testosterone and LH levels can help distinguish between different causes of abnormal sexual development:

- High testosterone and high LH: defective androgen receptor (androgen insensitivity syndrome)
- High testosterone and low LH: testosterone-secreting tumor
- Low testosterone and high LH: primary hypogonadism
- Low testosterone and low LH: hypogonadotrophic hypogonadism


a Primary hypogonadism
b Secondary hypogonadism
Hypothalamus
↑ GnRH
↓ GnRH
Anterior pituitary gland
↑ LH
↑ FSH
↓ LH
↓ = FSH
Testis
↓ Testosterone
↓ Testosterone




## Delayed puberty

The first visible sign of puberty in males is testicular enlargement, while in females it is breast development.

**Definition:** Absent or incomplete development of secondary sex characteristics by the age of 14 years in boys or 13 years in girls

**Causes**

- **Constitutional delay of growth and puberty (normal variants of growth): the most common cause of delayed puberty**
- **Primary/** hypergonadotrophic hypogonadism: e.g. Klinefelter's and Turner's syndromes.
- **Secondary/** hypogonadotrophic hypogonadism: causes
  - Genetic defects: (e.g., Kallmann syndrome, Prader-Willi syndrome, Gaucher disease)
  - Malnutrition (e.g., anorexia nervosa)

- Chronic diseases (e.g., inflammatory bowel disease, hypothyroidism, cystic fibrosis)

| Delayed puberty with short stature | Delayed puberty with normal stature |
|---|---|
| Turner's syndrome<br>Prader-Willi syndrome<br>Noonan's syndrome | polycystic ovarian syndrome androgen insensitivity<br>Kallman's syndrome<br>Klinefelter's syndrome |

## Features

**Signs of delayed puberty in girls include:**

- Absence of breast development by age 14 years
- Pubic hair absent by age 14
- More than five years between the start and completion of breast growth
- **Menarche has not occurred by age 16.**

**Signs of delayed puberty in boys include:**

- No testicular enlargement by age 14 years
- Pubic hair absent by age 15
- More than five years between the start and completion of growth of the genitalia.

## Diagnosis

**Primary hypogonadism** >> ↓ gonadal hormones (testosterone in boys and estradiol in girls) + ↑ luteinizing hormone (LH) and follicle-stimulating hormone (FSH).

**Secondary hypogonadism** >> ↓ hypothalamic gonadotropin-releasing hormone (GnRH) >> low to normal LH and FSH >> ↓ gonadal hormones

**Constitutional delay** is usually assessed using a **bone age assessment** (radiography of the hand and wrist) and measuring the patterns of ossification at the epiphyses of the bones of the hands >> delayed bone age.

## Management

- Constitutional delay: Observation
- Organic delay: Sex-steroid therapy to induce puberty + lifelong hormone replacement therapy after puberty

# Amenorrhoea

**primary amenorrhoea:**
defined as the failure to establish menstruation by **15 years** of age in girls with normal secondary sexual characteristics (such as breast development), or by 13 years of age in girls with no secondary sexual characteristics

**secondary amenorrhoea:**
cessation of menstruation for **3-6 months** in women with previously normal and regular menses, or 6-12 months in women with previous oligomenorrhoea

## Causes of primary amenorrhoea:

- **Turner's** syndrome: **Hypergonadotrophic** hypogonadism, short stature.
- **Kallmann's** syndrome (**hypogonadotrophic** hypogonadism).
- **Testicular feminisation syndrome**: good breast development in the absence of secondary sexual hair, with a history of hernias as a child (undescended testes). The vagina is blind ended, and there are no ovaries.
- **Congenital adrenal hyperplasia**
- Congenital malformations of the **genital** tract.
- **Anorexia nervosa** (**hypogonadotrophic** hypogonadism with mild ↑ prolactin).

## Causes of secondary amenorrhoea (after excluding pregnancy):

- **Hypothalamic amenorrhoea** (e.g. **Stress**, **excessive exercise**)
- Polycystic ovarian syndrome (PCOS)
- Hyperprolactinaemia
- Premature ovarian failure
- **Thyrotoxicosis**
- **Hypothyroidism** may also cause amenorrhoea
- Autoimmune hepatitis.

## Initial investigations:

- Exclude pregnancy with urinary or serum **βHCG.**
- Gonadotrophins (**FSH**): **low** levels indicate a **hypothalamic** cause whereas **raised** levels suggest an **ovarian** problem (e.g. premature ovarian failure).
- **Prolactin.**
- **Androgen** levels: raised levels may be seen in PCOS.
- **Oestradiol.**
- **Thyroid** function tests.

## Management

### primary amenorrhoea:

- investigate and treat any underlying cause
- with primary ovarian insufficiency due to gonadal dysgenesis (e.g. Turner's syndrome) are likely to benefit from hormone replacement therapy (e.g. to prevent osteoporosis etC)

### secondary menorrhoea

- exclude pregnancy, lactation, and menopause (in women 40 years of age or older)
- treat the underlying cause

hypothyroidism may also cause amenorrhoea

**NB:** In pregnancy: ↑ **Estradiol**, with **suppressed LH and FSH**, and ↑ **prolactin**
**NB:** Pregnancy would be associated with elevated oestradiol concentrations.

# Polycystic ovarian syndrome (PCOS)

Polycystic ovary syndrome (PCOS) is a complex condition of ovarian dysfunction, it is **extremely common**, thought to affect between **5-20% of women of reproductive age.**

PCOS is the most common cause of hyperandrogenism in women of reproductive age.

Management is complicated and problem based partly because the aetiology of PCOS is not fully understood.

Both **hyperinsulinaemia** and **high levels of LH** are seen in PCOS and there appears to be some overlap with the **metabolic syndrome.**

PCOs is associated with a **raised LH: FSH ratio >2**, with **insulin resistance** and **hyperandrogenism** as evidenced by **raised androstenedione, raised Serum dehydroepiandosterone sulphate (DHEAS)** and **slightly raised or normal testosterone but raised free androgen index.**

**Serum sex hormone binding globulin (SHBG)** is **lower** in PCOS. The reasons include that androgen reduce the globulin production, whereas oestrogen promotes production. It is a protein for transport of hormones in the blood.

**Elevated prolactin**, although a feature of PCOs, is **not specific** of the diagnosis and may suggest microprolactinoma.

Although insulin resistance is a feature of PCOs, a raised insulin concentration is rather irrelevant and no one would measure this in clinical

practice. It is often elevated in association with testosterone secreting tumours.

**The Rotterdam International Consensus Group described PCOS as a syndrome of ovarian dysfunction, characterised by hyperandrogenism and polycystic ovaries. They recommended that diagnosis be made if two of the following three criteria were met:**

- Oligomenorrhoea or anovulation.
- Clinical and/or biochemical evidence of hyperandrogenism.
- Polycystic ovaries on ultrasonography: multiple peripheral follicles with ovarian volume greater than 10 ml.

Other diseases which can cause similar symptoms, such as **androgen secreting tumours**, **Cushing's syndrome** and **congenital adrenal hyperplasia** must also be excluded.

## Features:

- Subfertility and infertility
- Menstrual disturbances (Irregular heavy periods) : oligomenorrhea and amenorrhoea
- Male pattern Hirsutism, acne (due to hyperandrogenism)
- Obesity
- **Acanthosis nigricans** (**due to insulin resistance**)
- **Clitoromegaly** is seen **occasionally** in PCOS but is normally associated with **very high androgen levels.** If clitoromegaly is found then **further investigations** to exclude **an ovarian** or **adrenal androgen secreting tumor** are required.

## Investigations:

- Pelvic ultrasound: **multiple cysts on the ovaries** which is **the most consistent feature** of PCOD: **the presence of at least 8 follicular cysts of less than 10 mm and increased ovarian stroma.**
- FSH, LH, prolactin, TSH, and testosterone are useful investigations:
- **Raised LH:FSH ratio > 2** is **a 'classical' feature** but is **no longer thought** to be useful in diagnosis.
- Prolactin may be normal or mildly elevated.
- **Testosterone may be normal or mildly elevated - however, if markedly raised consider other causes.**
- Check for impaired glucose tolerance.
- Typically in PCOS, **Oestradiol is normal or elevated** and a **low** oestradiol would be in keeping with **Cushing's.**

**N.B:** In PCOD >>> **multiple ovarian cysts by US** are the **most consistent feature**, however **Raised LH: FSH ratio** is a **'classical' feature** but is no longer thought to be useful in diagnosis.

It is recognised however that LH: FSH ratio is not always predictive of the presence of polycystic ovaries, **so for this reason abdominal ultrasound scan is the investigation of choice.**

**EX**: A 39-year-old woman comes to the clinic complaining of **excessive hairiness** and problems with **acne**. She also reports **increased libido** over the past few months. **Testosterone** is **8.9** nmol/L (N <2.5).

The most likely underlying diagnosis is >>> **Androgen secreting tumour >>> Abdominal ultrasound, CT or MRI** to elucidate whether an adrenal or ovarian tumour is the underlying cause.

The key here is the testosterone level, which is **more than 3 times the upper limit of normal**.

**Female patient with hirsutism, irregular periods and HTN:**
**1) PCOD**: so **LH/FSH ratio** is the 1st D.D of this patient.
**2) Cushing's syndrome**: the 2nd D.D.: ODST or 24 hrs urinary free cortisol.
**3) Cushing's disease**: by high-dose dexamethasone suppression test, only used if the ODST was previously positively suppressed. Then **plasma ACTH** and **MRI pituitary** are performed to localise the cause of the cortisol production once positive suppression test.

## DD for PCO:

- Cushing,
- Congenital adrenal hyperplasia

## Management:

### General

- weight reduction if appropriate
- if a women requires contraception then a combined oral contraceptive (COC) pill may help regulate her cycle and induce a monthly bleed

### Hirsutism and acne

- **a COC pill may be used help manage hirsutism. Possible options include a third generation COC which has fewer androgenic effects or** co-cyprindiol which has an anti-androgen action. Both of these types of COC may carry an increased risk of venous thromboembolism
- if **doesn't respond to COC then topical eflornithine may be tried**
- spironolactone, flutamide and finasteride may be used under specialist supervision

### Infertility

- **weight reduction if appropriate**
- the management of infertility in patients with PCOS should be supervised by a specialist. There is an ongoing debate as to whether metformin, **clomifene** or a combination should be used to stimulate ovulation
- a 2007 trial published in the New England Journal of Medicine suggested clomifene was the most effective treatment. There is a potential risk of multiple pregnancies with anti-oestrogen* therapies such as clomifene. The RCOG published an opinion paper in 2008 and concluded that on current evidence metformin is not a first line treatment of choice in the management of PCOS
- metformin is also used, either combined with clomifene or alone, particularly in patients who are obese
- gonadotrophins

**Infertility** in **PCOS >>> Clomifene** is superior to **metformin**

Clomiphene: works by occupying hypothalamic oestrogen receptors without activating them. This interferes with the binding of oestradiol and thus prevents negative feedback inhibition of FSH secretion.

**MRCPUK part 1 exam: H/O infertility with PCOS. Apart from advising her to lose weight, which intervention is most effective in increasing her chances of conceiving? Clomifene** (if clomifene – the first line - is not an option, metformin – the second line - is the right answer)

**MRCPUK part 1 exam: Which finding is most consistently seen in polycystic ovarian syndrome? Ovarian cysts on ultrasound**

**MRCPUK part 1 exam: What is the mechanism of action of metformin in PCOS? Increases peripheral insulin sensitivity**

## Hirsutism

hirsutism is often used to describe androgen-dependent hair growth in women

hypertrichosis used for androgen-independent hair growth

**Definition**: Excessive male pattern hair growth in women (e.g., on the chin, above the upper lip, and around the umbilicus)

## Causes

- idiopathic (the most common): normal menstrual cycle, normal serum androgen, and no identifiable cause hirsutism.
- Polycystic ovarian syndrome is **the most common causes of hirsutism**
- Excess androgen (10% of cases): hirsutism, acne, menstrual dysfunction, alopecia.
  - Cushing's syndrome
  - congenital adrenal hyperplasia
  - androgen therapy
  - obesity: due to peripheral conversion oestrogens to androgens
  - adrenal tumour
  - androgen secreting ovarian tumour
- drugs

## Assessment of hirsutism

- Mild hirsutism and normal menses >> do not require laboratory workup and can be treated empirically.
- Moderate or severe symptoms >> early morning **total testosterone** level
  - if moderately elevated, it should be followed by a plasma **free testosterone** level.
  - A total testosterone level greater than 200 ng per dl (6.94 nmol per L} should prompt evaluation for an androgen-secreting tumor.
- Testing for endocrinopathies and neoplasms, such as polycystic ovary syndrome, adrenal hyperplasia, thyroid dysfunction, Cushing syndrome, and androgen-secreting tumors.

## Management

- Advise weight loss if overweight
- Hair removal (Shaving)
- Pharmacologic measures
  - Combined oral contraceptive pills: **first-line pharmacologic treatment**
  - Facial hirsutism: topical eflornithine - contraindicated in pregnancy and breast- feeding
  - Treatment response should be monitored for at least six months before making adjustment.

## Hypertrichosis

**Definition:** excessive **hair growth above the normal** for the age, sex and race of an individual, in contrast to **hirsutism,** which is excess hair growth **in women** following a male distribution pattern.

### Causes

- drugs:
  - **phenytoin**
  - **minoxidil** (antihypertensive vasodilator. also used to treat androgenic alopecia → slows hair loss and promotes hair regrowth)
  - **ciclosporin**
  - diazoxide
- congenital hypertrichosis lanuginosa, congenital hypertrichosis terminalis
- metabolic disorders:
  - thyroid dysfunction,
  - porphyria cutanea tarda
  - anorexia nervosa

**Treatment:** Hair removal

## Androgen insensitivity syndrome (AIS)

Complete androgen insensitivity syndrome is the new term for **testicular feminization syndrome.**

Androgen insensitivity syndrome is an **X-linked recessive** condition due to **end-organ resistance to testosterone** causing **genotypically male children (46XY)** to have a **female phenotype.**

### Features:

- **'Primary amenorrhoea'.**
- **Undescended testes** causing **groin swellings.**
- **Normal breast development** may occur as a result of conversion of testosterone to oestradiol.
- Normal external **genitalia** they appear **female.**

### Diagnosis:

- **Buccal smear** or chromosomal analysis to reveal 46XY genotype.
- The serum testosterone is in the male range.

## Management:

- **Counselling - raise child as female**
- **Bilateral orchiectomy** (there is increased risk of testicular cancer due to undescended testes).
- **Oestrogen** therapy: **Diethyl-Stilboestrol (DES)** is a synthetic nonsteroidal estrogen has been associated with the induction of latent tumors and with influencing sexual behavior, but is not associated with abnormalities of sexual identity.

**EX:** A 16-year-old **female** patient is referred with **primary amenorrhoea**. Investigations reveal a 46 XY karyotype: **Androgen insensitivity syndrome**

# Premature ovarian insufficiency

Premature ovarian insufficiency is defined as the onset of menopausal symptoms and elevated gonadotrophin levels before the age of 40 years. It occurs in around 1 in 100 women.

## Causes of premature menopause include:

- idiopathic
  - the most common cause
  - there may be a family history
- bilateral oophorectomy
  - having a hysterectomy with preservation of the ovaries has also been shown to advance the age of menopause
- radiotherapy
- chemotherapy
- infection: e.g. mumps
- autoimmune disorders
- resistant ovary syndrome: due to FSH receptor abnormalities

**Features** are similar to those of the normal climacteric but the actual presenting problem may differ

- climacteric symptoms: hot flushes, night sweats
- infertility
- secondary amenorrhoea
- **raised FSH,** LH levels
  - e.g. FSH > 40 iu/l
  - elevated FSH levels should be demonstrated on 2 blood samples taken 4–6 weeks apart
- low oestradiol
  - e.g. < 100 pmol/l

## Management

- hormone replacement therapy **(HRT)** or a combined oral contraceptive pill should be offered to women until the age of the average menopause (51 years)
  - it should be noted that HRT does not provide contraception, in case spontaneous ovarian activity resumes

# Hormone replacement therapy

Hormone replacement therapy (HRT) involves the use of a small dose of oestrogen (combined with a progestogen in women with a uterus) to help alleviate menopausal symptoms.

## Side-effects

- nausea
- breast tenderness
- fluid retention and weight gain

## Potential complications

- **increased risk of breast cancer**
  - **increased by the addition of a progestogen**
  - in the Women's Health Initiative (WHI) study there was a relative risk of 1.26 at 5 years of developing breast cancer
  - the increased risk relates to the duration of use
  - the risk of breast cancer begins to decline when HRT is stopped and by 5 years it reaches the same level as in women who have never taken HRT
- **increased risk of endometrial cancer**
  - **oestrogen by itself should not be given as HRT to women with a womb**
  - reduced by the addition of a progestogen but not eliminated completely
  - the BNF states that the additional risk is eliminated if a progestogen is given continuously
- **increased risk of venous thromboembolism**
  - increased by the addition of a progestogen
  - transdermal HRT does not appear to increase the risk of VTE
  - NICE state women requesting HRT who are at high risk for VTE should be referred to haematology before starting any treatment (even transdermal)
- **increased risk of stroke**
- **increased risk of ischaemic heart disease if taken more than 10 years after menopause**

**summary:**

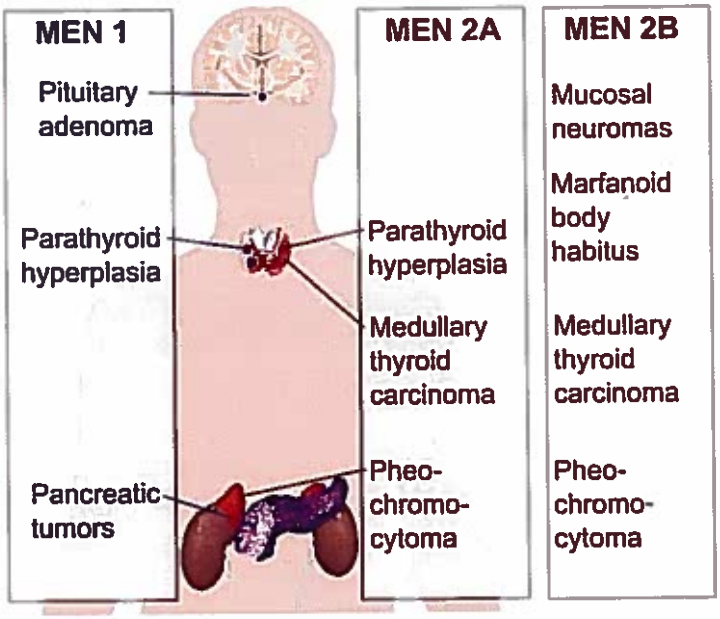
**Main indication for HRT: control of vasomotor symptoms**
**HRT: unopposed oestrogen increases risk of endometrial cancer**
**HRT: adding a progestogen increases the risk of breast cancer**

# IMPORTANT ENDOCRINE DISORDERS

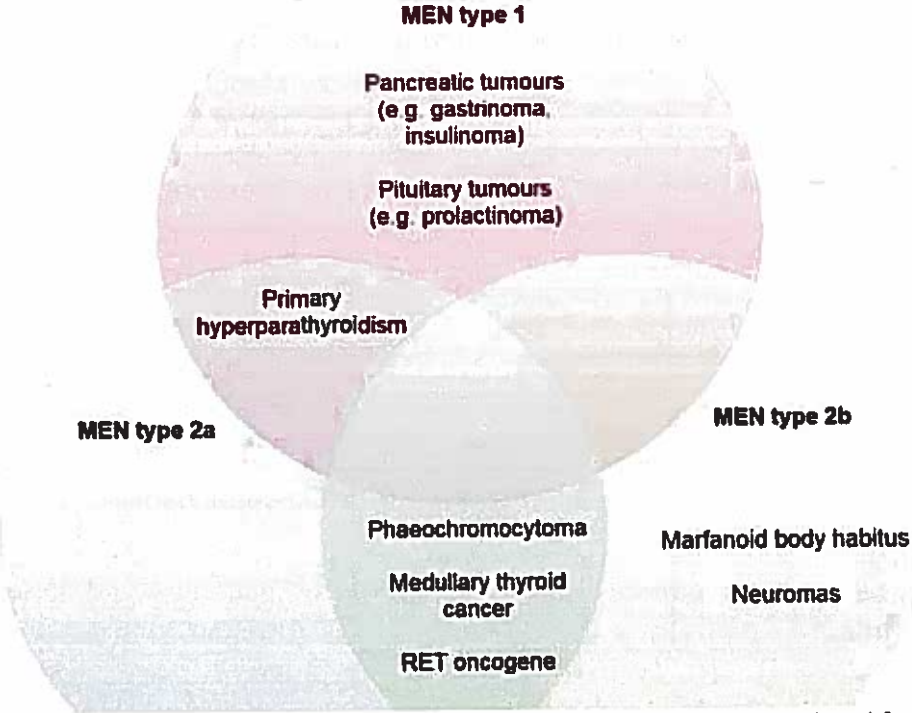
## Multiple Endocrine Neoplasia (MEN)

The table below summarises the three main types of multiple endocrine neoplasia (MEN). MEN is inherited as an autosomal dominant disorder.

| MEN type I | MEN type IIa | MEN type IIb |
|---|---|---|
| **Wermer Syndrome** | **Sipple Syndrome** | |
| **3 P's:**<br>➢ **P**arathyroid (95%): hyperparathyroidism due to parathyroid hyperplasia.<br>➢ **P**ituitary (70%): prolactinomas.<br>➢ **P**ancreas (50%): e.g. Insulinoma, Carcinoid, Gastrinoma (leading to recurrent peptic ulceration).<br>➢ Also: adrenal and thyroid. | ➢ **Medullary** thyroid cancer (MTC) (70%).<br>**2 P's:**<br>➢ **P**arathyroid (60%).<br>➢ **P**haeochromocytoma (95%). | ➢ **Medullary** thyroid cancer (MTC).<br>**1 P:**<br>➢ **P**haeochromocytoma.<br>➢ Marfanoid body habitus.<br>➢ Mucosal Neuromas.<br>➢ Medullated corneal nerve fibers.<br>➢ Intestinal polyps: (identified histologically as intestinal ganglio-neuromas and are usually asymptomatic). |
| MEN1 gene.<br>(On chromosome **11q13**)<br><br>Most common presentation = **hypercalcemia.** | **RET** oncogene.<br>(On chromosome 10) | **RET** oncogene.<br>(On chromosome 10) |




Multiple endocrine neoplasia (MEN) MEN 1: 3P
MEN 2A: 2P, 1M, MEN 2B: 1P, 3M (Keith Siau on Twitter)




Venn diagram showing the different types of MEN and their associated features.

**N.B:** MEN is inherited as an **autosomal dominant** disorder.

**N.B:** The high incidence of parathyroid tumours and hypercalcaemia make **serum calcium** a useful **indicator** of **MEN type 1** in suspected individuals (**90%** of patients with MEN type 1 have hypercalcaemia).

**N.B:** In **Phaeochromocytoma** and suspected MEN IIa >>> Check for **medullary carcinoma of the thyroid (C cell hyperplasia) firstly** then PTH by measuring **serum calcitonin** using **pentagastrin stimulation test**. If patients with MEN-2 are not identified by screening, often at the time of presentation **medullary thyroid carcinoma with metastases to cervical lymph nodes has already occurred.**

**NB:** In **MEN-2a** the initial diagnostic investigation of choice for pheochromocytoma is by **24 hr urinary catecholamine assay**, where the diagnosis is proven, it is sensible to screen for medullary thyroid carcinoma via **pentagastrin testing.**

**NB**: The **pentagastrin stimulation test** measures calcitonin levels at 2 and 5 minutes however, a rise in calcitonin is suggestive of medullary thyroid carcinoma. Elevated basal levels of calcitonin are not specific as are seen in pregnancy, carcinoid, pernicious anaemia, CRF and thyroiditis.

**NB: Renal disease** in **MEN-2** is characterised by **stone**, rather than tumour formation.

**RET** oncogene encodes a receptor tyrosine kinase & is associated with **MEN type II a & b.**

**EX**: Female Pt. with galactorrhoea + amenorrhea + Hypogonadotroghic hypogonadism (low FSH, LH, Estradiol) + High prolactin + Recurrent gastritis >>> MEN I

**EX**: Male 35 years old has ↑ **BP** 170/110 mmHg & ↑ **Ca** 3.1 mmol/L >> **MEN2A** , HTN is due to pheochromocytoma & high Ca is due to hyperparathyroidism.

MEN II A & B there is medullary thyroid cancer (MTC) and pheochromocytoma.
In MEN II B >>> In addition, there is characteristic facial appearance with swollen lips; tumours of the mucous membranes of the eyes, mouth, tongue and nasal cavity; enlarged colon; and skeletal abnormalities.

In **MEN-2b**, Intestinal **ganglioneuromatosis** affects around **75%** of cases. Neuromas involve the autonomic nerves of both the myenteric and submucosal plexi and can cause **poor suckling** with **failure to thrive**, **constipation**, **diarrhoea**, **recurrent pseudo-obstruction** and **toxic megacolon**.
In addition, **medullary thyroid carcinoma** is a feature of MEN-2b. This **metastases in early life**, and is therefore often **incurable by age 4 years** and leads to **early death**. **Total thyroidectomy** is the **only** established treatment for medullay thyroid carcinoma, the timing of which must take into account risks and benefits for small children.
**EX:** A 29-year-old woman brings her **6-week-old child**. She is concerned as the child has **poor suckling** and has been admitted to the ER on two occasions with **possible bowel obstruction** but later discharged. She tells you there is a **history in the family of a tumour 'syndrome'**, and one of her relatives died at a young age.
Which is the most likely underlying diagnosis >>> **MEN II b**

## Autoimmune Poly-endocrinopathy / Polyglandular Syndrome (APS)

**Addison's disease** (autoimmune hypoadrenalism) is associated with other endocrine deficiencies in approximately 10% of patients.

**There are 2 distinct types** of autoimmune polyglandular syndrome (APS):
**APS type 1:** It is occasionally referred to as **Multiple Endocrine Deficiency Autoimmune Candidiasis (MEDAC).** It is a **very rare autosomal recessive** disorder caused by **mutation of AIRE1 gene** on **chromosome 21.**

**Features** of APS type 1 **(2 or more of the following):**

- **Primary hypoparathyroidism (↓Ca):** in 90%
- **Addison's disease:** in 60%
- **Chronic mucocutaneous candidiasis** (typically **first** feature as young child).

These 3 major components of APS type 1 tend to present in the following chronological order of **candidiasis**, followed by **hypoparathyroidism**, followed by **adrenal insufficiency**.
**EX:** Pt with chronic mucocutaneous candidiasis and you suspect APS type I >>> check serum **Ca** and **Na & K**.

**TTT: Antifungals, Vit D, Calcium, Glucocorticoids** replacements.

**APS type 2:** (also referred to as **Schmidt's syndrome**) being **much more common.**

APS type 2 has a polygenic inheritance and is linked to HLA DR3/DR4.

**Patients have:**

- **Addison's disease** plus either:
  - **Type 1 DM or**
  - **Autoimmune thyroid disease (Hypothyroidism)**

**IF ALL 3 PRESENT CALLED CARPENTER SYNDROME**

**N.B: Vitiligo, Myasthenia gravis, primary hypogonadism coeliac disease** and **pernicious anaemia** can occur in both types of APS.
**However, to diagnose this syndrome there must be antbodies against each gland and tissue biopsy with infiltration by lymphocytes. othewise, patients with autoimmune disorders are more vulnerable to another one than general population.**

**N.B: Primary hypoparathyroidism (↓Ca)** is usually the first endocrine manifestation of type 1 autoimmune polyendocrinopathy syndrome. The contrast to multiple endocrine neoplasia (MEN), where **hyperparathyroidism (↑Ca)** is a common finding, should be noted.

**So,** Primary **HYPO**parathyroidism is usually the first endocrine manifestation of type I Autoimmune **POLY**endocrinopathy syndrome (APS).

While, in **MEN >>>>> HYPER**parathyroidism is the commonest finding.

**EX:** Female pt 35 years old with hypothyroidism on thyroxin replacement, she has nausea, vomiting, lethargy, postural hypotension, vitiligo, anaemia Hb=10 gm/dl, Na=124, K=4.5. >>> This is APS type 2.
In this case, if delay in arranging short synacthen test was likely, Adrenal autoantibodies are likely to be positive in over 80% of cases.
It is medical emergency and should start **hydrocortisone IV.**
This anaemia may raise possibility of pernicious anaemia or coeliac disease.

**EX:** Young woman 20 years with type 1 diabetes with **weight loss, lethargy** and **reduced insulin requirements** with **increasing frequency of hypoglycaemic events** >>> points to a general increase in insulin sensitivity and with her history of autoimmune disease (type 1 diabetes), **hypoadrenalism** should be considered as the cause >>> Hence, a **short Synacthen test** is the most appropriate diagnostic test.

**NB:** Associated hypothyroidism would cause weight gain.

# Carcinoid syndrome

## Features:

- **Flushing** (often **earliest** symptom) in **75-90%** of cases, often provoked by alcohol.
- **Hypotension**
- **Chronic diarrhoea** (in > **70%**).
- **Bronchospasm** (in **25%**).
- **Right heart valvular stenosis e.g. tricuspid / pulmonary stenosis is** found in **50%** of cases and can lead to right-sided CHF like LL oedema (left heart can be affected in bronchial carcinoid).
- **Pellagra** can rarely develop as dietary tryptophan is diverted to serotonin by the tumour.
- Other molecules such as ACTH and GHRH may also be secreted resulting in, for example, Cushing's syndrome.

The **triad** of **facial flushing, chronic diarrhoea** and **cardiac** involvement represents more than **85%** of symptoms of carcinoid syndrome.

## Investigations:

- **High 24-hour urinary 5-HIAA excretion**: (5-hydroxyindoleacetic acid) - is greater than 0.3 mmol.
- **Abdominal US:** to visualise the liver metastasis.
- **Chest and abdomen CT**
- Plasma chromogranin A y

## Management: (mainly palliative):

- **Somatostatin** analogues e.g. **Octreotide**
- **Symptomatic** control, as diarrhoea: cyproheptadine may help
- Surgery to debulk the tumour
- Trans-arterial embolisation and radioisotope therapy.

**EX:** A 65-year-old man known to have a carcinoid tumour of the appendix is found to have hepatic metastases. If the patient develops carcinoid syndrome, what is the first symptom most likely to occur? >>> **Flushing.**

# PANCREATIC DISORDERS

## Pancreatic Hormones

- Islet **A** cells produce **glucagon**
- **Islet beta cells produce:**
  - **Insulin**
  - **C peptide**
  - **pro-insulin**
  - **amylin**
  - **GABA**
- Islet **D** cells produce **somatostatin**
- **F** cells produce **pancreatic polypeptide**

## Glucose transporters

### Glucose entrance to the cells

- To intestinal epithelial cells and proximal renal tubular cells >> via Sodium/Glucose cotransporter (**SGLT**)
- To all other cells of the body >> **G**lucose **T**ransporters (**GLUTs**).

### Sodium/glucose cotransporter (SGLT)

**Glucose uptake into** the enterocyte from the lumen of the GI tract occurs primarily via the sodium-dependent **SGLT-1** secondary active transport mechanism.

- SGLT-1 is a transporter found predominantly in the gut, and is responsible for glucose absorption.
- The Na+-glucose cotransporter also transports galactose. Thus, when the cotransporter is congenitally defective, the resulting glucose and galactose malabsorption causes severe diarrhea that can be fatal if glucose and galactose are not removed from the diet.

**Function**

- **transport glucose actively across lumen against concentration gradient**
  - energy provided by transport of sodium down its concentration gradient

**Location**

- **small intestine** (**SGLT1**) >> 2:1 $Na^+$: Glu
- **proximal tubule of nephron** (**SGLT2**) >> 1:1 $Na^+$: Glu

**Glucose exit from the enterocyte into** the extracellular fluid occurs by facilitated diffusion and is mediated by the membrane transporter, **Glut-2**.

## Glucose transporters (GLUTs)

### GLUT-1

#### Function

basal glucose uptake (GLUT1 and GLUT3 continually transport glucose into cells at an essentially constant rate.)

- high affinity
  - transporters saturated at normal blood glucose levels
  - ensures glucose entry to cells

#### Location

- **wide distribution** in tissues in the body (brain, erythrocytes, endothelial cells, cornea **etc.)**
- especially expressed in cells with barrier functions, such as Blood-Brain barrier, blood-retinal barrier, blood placental barrier, blood testes barrier
- **most importantly it is expressed in erythrocytes.**

### GLUT-2

- GLuT 2 is a glucose transporter expressed in **pancreatic beta cells**.
- It is a fundamental part of the glucose sensing apparatus in the pancreatic beta cells and helps trigger insulin release in response to increasing glucose concentrations in the extracellular fluid.
- GluT 2 is also expressed in hepatocytes and may act as a glucose sensor in the portal vein system.
- It may have a role in regulating glucagon secretion and feeding behaviour.

#### Function

- **low affinity glucose uptake** (high-capacity but a low affinity transporter)
  - in the fasting state glucose does not enter cells
  - mediates glucose surplus storage in liver when blood glucose levels rise
  - **facilitates insulin release in β-cells**

#### Location

- hepatocytes
- **pancreatic β-cells**
- kidney
- small intestines

In healthy individuals, which glucose transporter is required for triggering insulin secretion in response to elevated blood glucose concentration?
**>> GluT 2**

### GLUT-3

**Function**

- high affinity glucose uptake
  - glucose preferentially accessed by neurons in low-glucose states

**Location**

- **brain**
- **neurons**

### GLUT-4

**GLUT-4 is the only glucose transporter that is responsive to circulating insulin levels.**

- ↑plasma glucose concentration >> ↑**circulating insulin** >> ↑expression of GLUT-4 >> ↑glucose transport into the cell.
- The other types of glucose receptors (GLUT-1,2,3, & 5) are not responsive to circulating insulin levels
- exogenous insulin in the treatment of diabetes mellitus results in increased glucose uptake **via the GLUT-4 transporter.**
- This high-affinity glucose transporter plays a crucial role in avoiding postprandial hyperglycemia, since insulin secreted by the pancreatic beta cells promotes glucose uptake into myocytes.

**Function**

- **insulin-controlled uptake of glucose**
- basal level of glucose intake without insulin
  - presence of insulin ↑ translocation of transporters to the cell membrane
    - ↑↑↑ glucose uptake
    - **also stimulated by exercise**

**Location**

- **adipocytes**
- **myocytes**
- **cardiomyocytes**

| Which glucose transporter is responsible for assisting glucose across the plasma membrane in myocytes? **>> GLUT 4** |
|---|

### Glut-5

- **Located** on the apical portion of the enterocyte
- **Function**: entry of **fructose** into the cell.

- GLUT-1 = BBB (Blood- Brain barrier)
- GLUT-3 = "Brain"

# Diabetes mellitus

## Pathophysiology

### Type 1 DM:

- **Autoimmune** disease.
- Type 1 DM is a primarily **T cell mediated disorder.** Whilst autoantibodies to beta cell antigens are measurable in patients with the disease, they are not thought to play direct role in its pathogenesis.
- **Antibodies** against beta cells of pancreas.
- Various antibodies such as islet-associated antigen **(IAA) antibody** and glutamic acid decarboxylase **(GAD) antibody** are detected in patients **who later** go on to develop T 1 DM - their prognostic significance is not yet clear.
- Anti-IA2 and anti-GAD Abs are measured to support the diagnosis.
- **Only 10%** of patients have a **positive family history.**
- **Identical twins** show **a genetic concordance of 40%.**
- **HLA DR4** > HLA DR3.
- It is inherited in **a polygenic fashion.**
- **Enteroviruses** may play a role in both protection from and susceptibility to T1DM.
- The presence of **GAD** autoantibodies would signify an autoimmune etiology and their presence signifies a 10 fold increased risk of developing IDDM, **being found in 70-90% of type1 diabetics**. This would be a case of latent autoimmune diabetes in adults (**LADA**) and constitutes approximately 10% of patients incorrectly labelled as T2DM.
- The most closely associated with the imminent development of DM T1 is **loss of first phase insulin response** which is an indicator of significant impending beta cell destruction.

### Type 2 DM:

- It is thought to be caused by a relative deficiency of insulin and the phenomenon of insulin resistance.
- A reduction in beta cell mass due to **amyloid** deposition may partly account for this.
- The presence of **amyloid polypeptide** on pancreatic histology is highly suggestive of type **2** DM.
- Age, obesity and ethnicity are important aetiological factors.
- There is almost **100% concordance in identical twins** and **no HLA associations.**

## Summary of types of diabetes:

| Type | Notes |
|---|---|
| **Type 1 diabetes mellitus (T1DM)** | Autoimmune disorder where the insulin-producing beta cells of the islets of Langerhans in the pancreas are destroyed by the immune system<br>This results in an absolute deficiency of insulin resulting in raised glucose levels<br>Patients tend to develop T1DM in childhood/early adult life and typically present unwell, possibly in diabetic ketoacidosis |
| **Type 2 diabetes mellitus (T2DM)** | This is the most common cause of diabetes in the developed world. It is caused by a relative deficiency of insulin due to an excess of adipose tissue. In simple terms there isn't enough insulin to 'go around' all the excess fatty tissue, leading to blood glucose creeping up. |
| **Prediabetes** | This term is used for patients who don't yet meet the criteria for a formal diagnosis of T2DM to be made but are likely to develop the condition over the next few years. They, therefore, require closer monitoring and lifestyle interventions such as weight loss |
| **Gestational diabetes** | Some pregnant develop raised glucose levels during pregnancy. This is important to detect as untreated it may lead to adverse outcomes for the mother and baby |
| **Maturity onset diabetes of the young (MODY)** | A group of inherited genetic disorders affecting the production of insulin. Results in younger patients developing symptoms similar to those with T2DM, i.e. asymptomatic hyperglycaemia with progression to more severe complications such as diabetic ketoacidosis |
| **Latent autoimmune diabetes of adults (LADA)** | The majority of patients with autoimmune-related diabetes present younger in life. There are however a small group of patients who develop such problems later in life. These patients are often misdiagnosed as having T2DM |
| **Other types** | Any pathological process which damages the insulin-producing cells of the pancreas may cause diabetes to develop. Examples include chronic pancreatitis and haemochromatosis.<br>Drugs may also cause raised glucose levels. A common example is glucocorticoids which commonly result in raised blood glucose levels |

## Symptoms and signs

The presentation of diabetes mellitus depends very much on the type:

| Type 1 DM | Type 2 DM |
|---|---|
| Weight loss<br>Polydipsia<br>Polyuria<br>May present with diabetic ketoacidosis<br>• abdominal pain<br>• vomiting<br>• reduced consciousness level | Often picked up incidentally on routine blood tests<br>Polydipsia<br>Polyuria |

Remember that the polyuria and polydipsia are due to water being 'dragged' out of the body due to the osmotic effects of excess glucose

## Investigations

There are 4 main ways to check blood glucose:

- a finger-prick bedside glucose monitor
- a one-off blood glucose. This may either be fasting or non-fasting
- a HbA1c. This measures the amount of glycosylated haemoglobin and represents the average blood glucose over the past 2-3 months
- a glucose tolerance test. In this test, a fasting blood glucose is taken after which a 75g glucose load is taken. After 2 hours a second blood glucose reading is then taken

**Diagnosis of DM:** symptoms + fasting ≥ 7.0, random ≥ 11.1 - if asymptomatic need two readings.

**The diagnosis of diabetes requires (WHO guidelines):**

- **Fasting** plasma glucose **≥ 7.0** mmol/l (≥125 mg/dl).
- **Random** plasma glucose **≥ 11.1** mmol/l (≥200 mg/dl)
- **75 g OGTT two hour** plasma glucose **≥ 11.1** mmol/l (≥200 mg/dl)

**If the patient is asymptomatic** the above criteria **apply** but **must** be demonstrated on **TWO confirmatory samples on separate occasions.**.
The American Diabetes Association (ADA) has recently added another criterion:

- **HbA1c >6.5%** or **48** mmol/mol.

In 2011 WHO released supplementary guidance on the use of HbA1c on the diagnosis of diabetes:

- **A HbA1c of greater than or equal to 6.5% (48 mmol/mol) is the cut-off point for a diagnosis of diabetes mellitus.**
- **A HbAlc value of less than 6.5% does not exclude diabetes** (i.e. it is not as sensitive as **fasting samples** for detecting diabetes).

- In patients **without symptoms**, the test must be **repeated** to confirm the diagnosis.
- It should be remembered that **misleading HbA1c** results can be caused by increased RBCs turnover (as in anaemia, haemoglobinopathies and pregnancy).

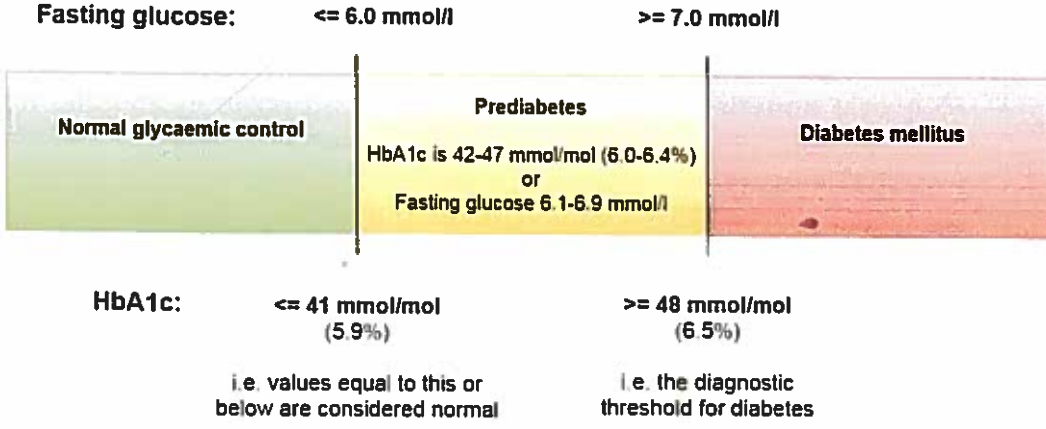



Diagram showing the spectrum of diabetes diagnosis

## Management

The principle of managing diabetes mellitus are as follows:

- drug therapy to normalise blood glucose levels
- monitoring for and treating any complications related to diabetes
- modifying any other risk factors for other conditions such as cardiovascular disease

### Type 1 diabetes

- patients always require insulin to control the blood sugar levels. This is because there is an absolute deficiency of insulin with no pancreatic tissue left to stimulate with drugs
- different types of insulin are available according to their duration of action

### Type 2 diabetes

- the majority of patients with type 2 diabetes are controlled using oral medication
- the first-line drug for the vast majority of patients is metformin
- second-line drugs include sulfonylureas, gliptins and pioglitazone. Please see the table below for further information
- if oral medication is not controlling the blood glucose to a sufficient degree then insulin is used

## OGTT (Oral Glucose Tolerance Test)

The OGTT has been used for many decades to diagnose diabetes. The test requires:

- **Overnight fast** prior to the test.
- Normal eating the previous day.
- **Baseline sample** for glucose using a fluoride tube.
- **75 g oral anhydrous glucose** usually washed down in **250-300 ml water** (if hydrous glucose is used, the same weight represents a lower proportion of glucose in molar measurement).
- Further glucose **sample taken at 120 minutes.**
- **Plasma tubes**, such as **fluoride oxalate**, must be used as the test results have not been validated using serum samples.
- Serum samples without additives allow further metabolism of the glucose by the red cells and may give a falsely low value. Fluoride oxalate prevents further metabolism of glucose.

The OGTT test has poor reproducibility but is particularly useful in cases of **borderline diabetes** or **gestational diabetes**.

## Impaired Glucose Regulation (IGR)

Impaired glucose regulation (**IGR**) may also be referred to as non-diabetic hyperglycaemia (**NDH**) or **prediabetes**.

It describes blood glucose levels which are above the normal range but not high enough for a diagnosis of diabetes mellitus.

Diabetes UK estimate that around **1 in 7 adults in the UK** have IGR.

Many individuals with IGR **will progress on to developing T2DM** and they are therefore at greater **risk** of **microvascular** and **macrovascular** complications.

**There are two main types of IGR:**

1) Impaired fasting glucose (IFG) - due to **hepatic** insulin resistance.
2) Impaired glucose tolerance **(IGT)** - due to **muscle** insulin resistance.

Patients with **IGT** are **more likely** to develop **T2DM** and **cardiovascular disease than** patients with IFG.

The absolute **risk of progression from IGT** to **type 2 DM** is **33 % over 6 years** follow up. This increased to 65% if individuals had both IGT and IFG.

**Triglycerides** is the **strongest independent** predictor of **cardiovascular death** in a patient with **impaired glucose tolerance IGT,** ahead of other more established risk factors such as smoking, body weight or blood pressu9re.

## Definitions:

**Impaired fasting glucose (IFG):** A **fasting** glucose **from 6.1 to 7.0** mmol/l. (= from 110 to 125 mg/dl).

**Impaired glucose tolerance (IGT):** A **fasting** plasma glucose < 7.0 mmol/l and **OGTT 2-hour value** from **7.8** mmol/l to 11.1 mmol/l (= from 140 to 200 mg/dl).

- The role of HbA1c is diagnosing IGR and diabetes is currently under review.
- People with **IFG** should then be offered **an oral glucose tolerance test (OGTT)** to rule out a diagnosis of diabetes. A result below 11.1 mmol/l but above 7.8 mmol/l indicates that the person doesn't have diabetes but does have IGT. A 2 hour value of equal to or over 11.1 mmol/L is diagnostic of diabetes.

**Identification of patients with prediabetes**

- NICE recommend using a validated computer based risk assessment tool for all adults aged 40 and over, people of South Asian and Chinese descent aged 25-39, and adults with conditions that increase the risk of type 2 diabetes
- patients identified at high risk should have a blood sample taken
- a fasting plasma glucose of 6.1-6.9 mmol/l or an HbA1c level of 42-47 mmol/mol (6.0-6.4%) indicates high risk

## Management:

- Diabetes UK suggests using the term '**prediabetes**' when discussing the condition with patients as research has shown that this term has the most impact and is most easily understood and the term of **impaired glucose regulation (IGR)** when talking to other healthcare professionals.
- **Lifestyle modification**: weight loss, increased exercise, change in diet.
- At least yearly follow-up with blood tests is recommended.

**EX:** Patient with **Fasting** glucose **6.6** mmol/l >> Impaired fasting glucose (IFG) >> **hepatic** insulin resistance.

**Which drug classes is most well known as a cause of impaired glucose tolerance? >> Atypical antipsychotics**

# Glycosylated haemoglobin (HbA1c)

Glycosylated haemoglobin (HbA1c) is the most widely used measure of long-term glycaemic control in diabetes mellitus.
HbA1c is produced by the glycosylation of haemoglobin at a rate proportional to the glucose concentration.

**The level of HbA1c therefore is dependant on:**

1) Red blood cell lifespan
2) Average blood glucose concentration

A number of conditions can interfere with accurate HbA1c interpretation:

| Lower-than-expected levels of HbA1c (due to reduced RBCs lifespan) | Higher-than-expected levels of HbA1c (due to increased RBCs lifespan) |
|---|---|
| ➢ Sickle-cell anaemia.<br>➢ GP6D deficiency.<br>➢ Hereditary spherocytosis.<br>➢ Chronic liver disease.<br>➢ Splenomegaly<br>➢ Hypertriglyceridemia. | ➢ Iron-deficiency anaemia.<br>➢ Vitamin B12/folic acid def.<br>➢ Alcohol dependence.<br>➢ CRF<br>➢ Hyperbilirubinaemia.<br>➢ Splenectomy. |

HbA1c is generally thought to reflect the blood glucose over the **previous '2-3 months'**, although there is some evidence it is weighed more strongly to glucose levels of the past 2-4 weeks.

The relationship between HbA1c and average blood glucose is complex but has been studied by the Diabetes Control and Complications Trial (DCCT).

A new internationally standardized method for reporting HbA1c has been developed by the International Federation of Clinical Chemistry (IFCC). This will report **HbA1c in mmol per mol of hemoglobin** without glucose attached.

| HBA1c (%) | Average plasma glucose (mmol/l) | IFCC-HbA1c (mmol/mol) |
|---|---|---|
| 5 | 5.5 | |
| 6 | 7.5 | 42 |
| 7 | 9.5 | 53 |
| 8 | 11.5 | 64 |
| 9 | 13.5 | 75 |
| 10 | 15.5 | |
| 11 | 17.5 | |
| 12 | 19.5 | |

**N.B:** From the above mentioned table we can see that:
**Average plasma glucose = (2 * HbA1c) - 4.5**

**NB:** Compared with subjects with normoglycemia, **beta cell mass** is **reduced:**
- By **50%** in subjects with **Impaired Fasting Glucose**,
- By **65%** in subjects with **Type 2** diabetes, and
- **Over 90%** in subjects with **type 1** diabetes.

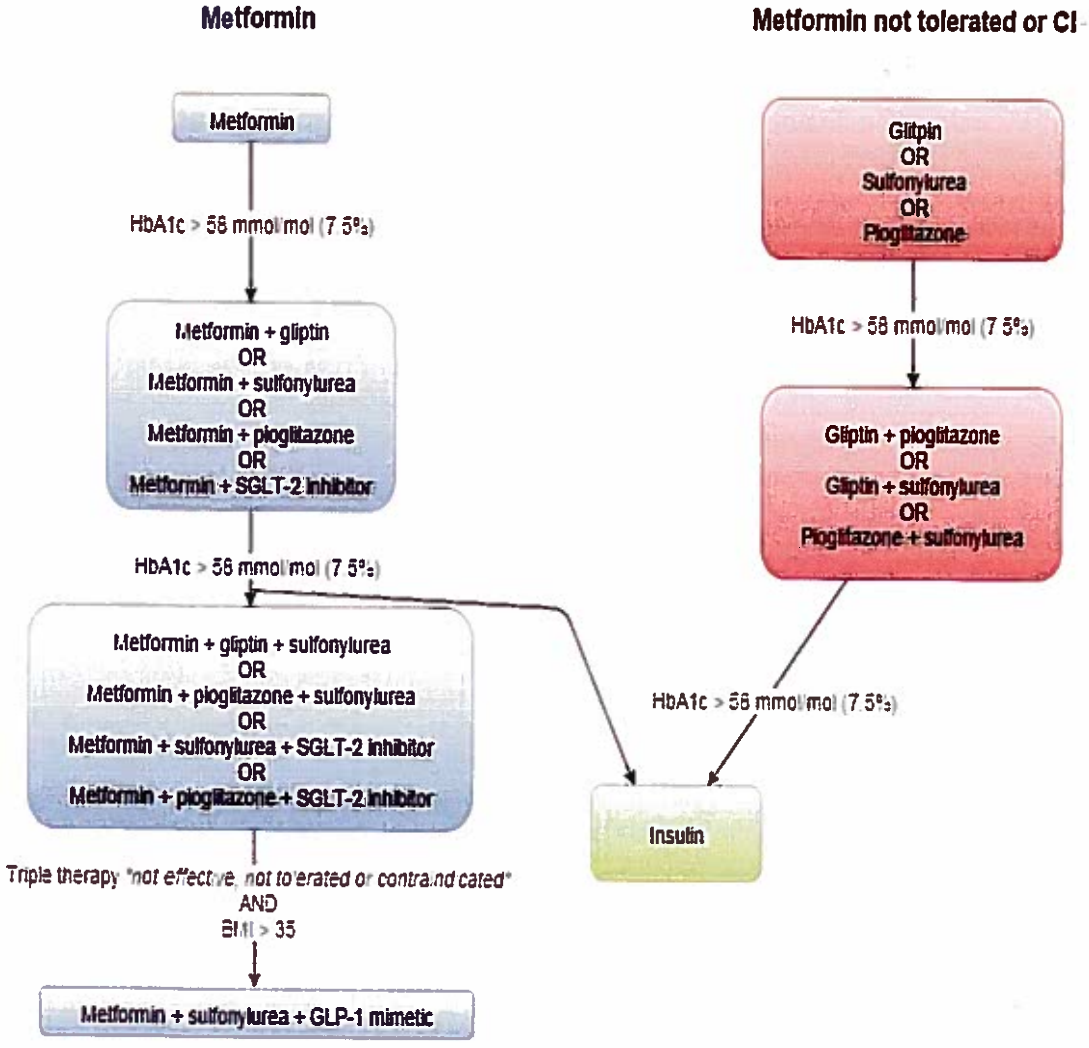
The suggestion therefore is one of gradual insulin deficiency associated with increasing insulin resistance.

# Drugs in diabetes

The table below shows some of the main drugs used in the management of diabetes mellitus:

| Drug class | Mechanism of action | Route | Main side-effects | Notes |
|---|---|---|---|---|
| **Insulin** | Direct replacement for endogenous insulin | Subcutaneous | Hypoglycaemia<br>Weight gain<br>Lipodystrophy | Used in all patients with T1DM and some patients with poorly controlled T2DM<br><br>Can be classified according to source (analogue, human sequence and porcine) and duration of action (short, immediate, long-acting) |
| **Metformin** | Increases insulin sensitivity<br>Decreases hepatic gluconeogenesis | Oral | Gastrointestinal upset<br>Lactic acidosis* | First-line medication in the management of T2DM<br><br>Cannot be used in patients with an eGFR of < 30 ml/min |
| **Sulfonylureas** | Stimulate pancreatic beta cells to secrete insulin | Oral | Hypoglycaemia<br>Weight gain<br>Hyponatraemia | Examples include gliclazide and glimepiride |
| **Thiazolidinediones** | Activate PPAR-gamma receptor in adipocytes to promote adipogenesis and fatty acid uptake | Oral | Weight gain<br>Fluid retention | Only currently available thiazolidinedione is pioglitazone |
| **DPP-4 inhibitors (-gliptins)** | Increases incretin levels which inhibit glucagon secretion | Oral | Generally well tolerated but increased risk of pancreatitis | |
| **SGLT-2 inhibitors (-gliflozins)** | Inhibits reabsorption of glucose in the kidney | Oral | Urinary tract infection | Typically result in weight loss |
| **GLP-1 agonists (-tides)** | Incretin mimetic which inhibits glucagon secretion | Subcutaneous | Nausea and vomiting<br>Pancreatitis | Typically result in weight loss |

## NICE provide guidelines on how drug therapy should be used in T2DM:



# Diabetes mellitus: management of type 1

## HbA1c

- should be monitored every 3-6 months
- adults should have a target of HbA1c level of 48 mmol/mol (6.5%) or lower. NICE do however recommend taking into account factors such as the person's daily activities, aspirations, likelihood of complications, comorbidities, occupation and history of hypoglycaemia

## Self-monitoring of blood glucose

- recommend testing at least 4 times a day, including before each meal and before bed
- more frequent monitoring is recommended if frequency of hypoglycaemic episodes increases; during periods of illness; before, during and after sport; when planning pregnancy, during pregnancy and while breastfeeding

## Blood glucose targets

- 5-7 mmol/l on waking and
- 4-7 mmol/l before meals at other times of the day

## Type of insulin

- **offer multiple daily injection basal–bolus insulin regimens**, rather than twice-daily mixed insulin regimens, as the insulin injection regimen of choice for all adults
- twice-daily insulin detemir is the regime of choice. Once-daily insulin glargine or insulin detemir is an alternative
- offer rapid-acting insulin analogues injected before meals, rather than rapid-acting soluble human or animal insulins, for mealtime insulin replacement for adults with type 1 diabetes

## Metformin

- **NICE recommend considering adding metformin if the BMI >= 25 kg/m²**

## Targets

| Test | Targets |
|---|---|
| HbA1c | ≤ 48 mmol/mol (6.5%) |
| fasting plasma glucose | 5–7 mmol/litre **on waking** |
| | 4–7 mmol/litre **before meals** |
| **plasma glucose at least 90 minutes after eating** | **5–9 mmol/litre** |
| during surgery or acute illness | 5–8 mmol/litre |
| blood pressure | 135/85 mmHg |

# Diabetes mellitus: management of type 2

NICE updated its guidance on the management of (T2DM) IN 2020:

It's worthwhile thinking of the average patient who is taking metformin for T2DM,
you can titrate up metformin and encourage lifestyle changes to aim for a HbA1c of 48 mmol/mol (6.5%),
but should only add a second drug if the HbA1c rises to 58 mmol/mol (7.5%)

**Dietary advice:**

- Encourage high fiber, low glycemic index sources of carbohydrates.
- Include low-fat dairy products and oily fish.
- Control the intake of foods containing saturated fats and trans-fatty acids.
- Limited substitution of sucrose-containing foods for other carbohydrates is allowable, but care should be taken to avoid excess energy intake.
- **Discourage use of foods marketed specifically at people with diabetes.**
- Initial target weight loss in an overweight person is 5-10%.

**HbA1c:**

- The general target for patients is **48** mmol/mol (DCCT = **6.5%**).
- HbA1c levels below 48 mmol/mol (DCCT = 6.5%) should not be pursued.
- However, individual targets should be agreed with patients to encourage motivation.
- HbA1c should be checked **every 3-6 months until stable, then 6 monthly.**

**Blood pressure:**

- Target BP is < 140/80 mmHg.
- if end-organ damage is present target should be < 130/80 mmHg.
- **ACEIs** or **ARBs** are first-line.

**The NICE treatment algorithm** has become much more complicated following the introduction of new therapies for type 2 diabetes.

- NICE still suggest a trial of lifestyle interventions first (many local protocols now recommend in adults with type 2 diabetes, **if metformin is contraindicated or not tolerated**, consider initial drug treatment with:
- a dipeptidyl peptidase-4 (DPP-4) inhibitor or
- pioglitazone or

- a sulfonylurea.
- Be aware that, if metformin is contraindicated or not tolerated, repaglinide is both clinically effective and cost effective in adults with type 2 diabetes. However, discuss with any person for whom repaglinide is being considered, that there is no licensed non-metformin-based combination containing repaglinide that can be offered at first intensification
- Do not forget to add vitamin B12 supplementation if you are going to prescribe metformin for longer time (more than 3 years) or in high doses
- **Sulphonylurea** can be used as first-line if the patient is not overweight, metformin is contraindicated or not tolerated, or a rapid response to therapy is required.
- The addition of either **sulphonylureas or insulin** at step two.
- It does not recommend use of older first generation sulphonylureas such as chlorpropamide or glibenclamide (Daonil®), instead recommending use of **newer** agents such as **gliclazide (Diamicron®), glimepiride (Amaryl®)** or **glipizide (MiniDiab®)**.
- Glibenclamide (Daonil®) is long-acting SU and likely to increase the risk of hypoglycaemia and hence "funny turns".
- Maximum daily dose of **Diamicron** is **160 mg**, **Amryl** is **6 mg**.
- **If the patient is at risk from hypoglycaemia** (or the consequences of) (e.g. a **driver**) then a **DPP-4 inhibitor** or **thiazolidinedione (TZD)** should be considered rather than a sulfonylurea.
- **If patient is intolerant to metformin >>> use TZD (Pioglitazone).**
- **Meglitinides e.g. Repaglinide (Novonorm®)** (insulin secretagogues):
  - Like sulfonylureas they bind to an **ATP-dependent K+ (KATP) channel** on the cell membrane of pancreatic beta cells.
  - Should be considered for patients with an **erratic lifestyle.**
  - They are particularly useful for **post-prandial hyperglycaemia.** Patients take them **shortly before meals.**
  - Adverse effects include weight gain and hypoglycaemia (but less than sulfonylureas).
- **If HbA1c > 7.5% then consider human insulin.**
- **Metformin treatment should be continued after starting insulin.**
- **Exenatide** should be used **only**
  1 **when insulin would otherwise be started.** or
  2. **Obesity** is a problem (BMI > 35 kg/m2). And /or
  3. The **need for high dose insulin** is likely.

- **Continue only if beneficial response** occurs and is maintained **(> 1.0 %** percentage point HbA1c reduction in 6 months and **weight loss > 3% at 6 months).**
- (I.e. No: exenatide plus insulin at the same regimen in T2DM. Exenatide should only be used in combination with metformin, a sulfonylurea or both).

**Lifestyle or single drug treatment**

| Management of T2DM | HbA1c target |
|---|---|
| Lifestyle | 48 mmol/mol (6.5%) |
| Lifestyle + metformin | 48 mmol/mol (6.5%) |
| Includes any drug which may cause hypoglycaemia (e.g. lifestyle + sulfonylurea) | 53 mmol/mol (7.0%) |

**Practical examples**

- a patient is newly diagnosed with HbA1c and wants to try lifestyle treatment first. You agree a target of 48 mmol/mol (6.5%)
- you review a patient 6 months after starting metformin. His HbA1c is 51 mmol/mol (6.8%). You increase his metformin from 500mg bd to 500mg tds and reinforce lifestyle factors

**Patient already on treatment**

| Management of T2DM | HbA1c target |
|---|---|
| Already on one drug, but HbA1c has risen to 58 mmol/mol (7.5%) | 53 mmol/mol (7.0%) |

## Drug treatment

NICE guidelines introduced some changes into the management of type 2 diabetes. There are essentially two pathways, one for patients who can tolerate metformin, and one for those who can't:

**Tolerates metformin:**

- metformin is still first-line and should be offered if the HbA1c rises to 48 mmol/mol (6.5%) * on lifestyle interventions
- if the HbA1c has risen to 58 mmol/mol (7.5%) then a second drug should be added from the following list:
  1. sulfonylurea
  2. gliptin
  3. pioglitazone
  4. SGLT-2 inhibitor

- if despite this the HbA1c rises to, or remains above 58 mmol/mol (7.5%) then triple therapy with one of the following combinations should be offered:
  1. metformin + gliptin + sulfonylurea
  2. metformin + pioglitazone + sulfonylurea

3. metformin + sulfonylurea + SGLT-2 inhibitor
4. metformin + pioglitazone + SGLT-2 inhibitor
5. OR insulin therapy should be considered

### Criteria for glucagon-like peptide1 (GLP1) mimetic (e.g., exenatide)

- if triple therapy is not effective, not tolerated or contraindicated then NICE advise that we consider combination therapy with metformin, a sulfonylurea and a glucagon-like peptide1 (GLP1) mimetic if:
  1. BMI >= 35 kg/m² and specific psychological or other medical problems associated with obesity or
  2. BMI < 35 kg/m² and for whom insulin therapy would have significant occupational implications or weight loss would benefit other significant obesity-related comorbidities
- only continue if there is a reduction of at least 11 mmol/mol [1.0%] in HbA1c and a weight loss of at least 3% of initial body weight in 6 months

### Practical examples

- you review an established type 2 diabetic on maximum dose metformin. Her HbA1c is 55 mmol/mol (7.2%). You do not add another drug as she has not reached the threshold of 58 mmol/mol (7.5%)
- a type 2 diabetic is found to have an HbA1c of 62 mmol/mol (7.8%) at annual review. They are currently on maximum dose metformin. You elect to add a sulfonylurea

### Cannot tolerate metformin or contraindicated

- if the HbA1c rises to 48 mmol/mol (6.5%) on lifestyle interventions, consider one of the following:
  - sulfonylurea
  - gliptin
  - pioglitazone
- if the HbA1c has risen to 58 mmol/mol (7.5%) then a one of the following combinations should be used:
  - gliptin + pioglitazone
  - gliptin + sulfonylurea
  - pioglitazone + sulfonylurea
- if despite this the HbA1c rises to, or remains above 58 mmol/mol (7.5%) then consider insulin therapy

### Starting insulin:

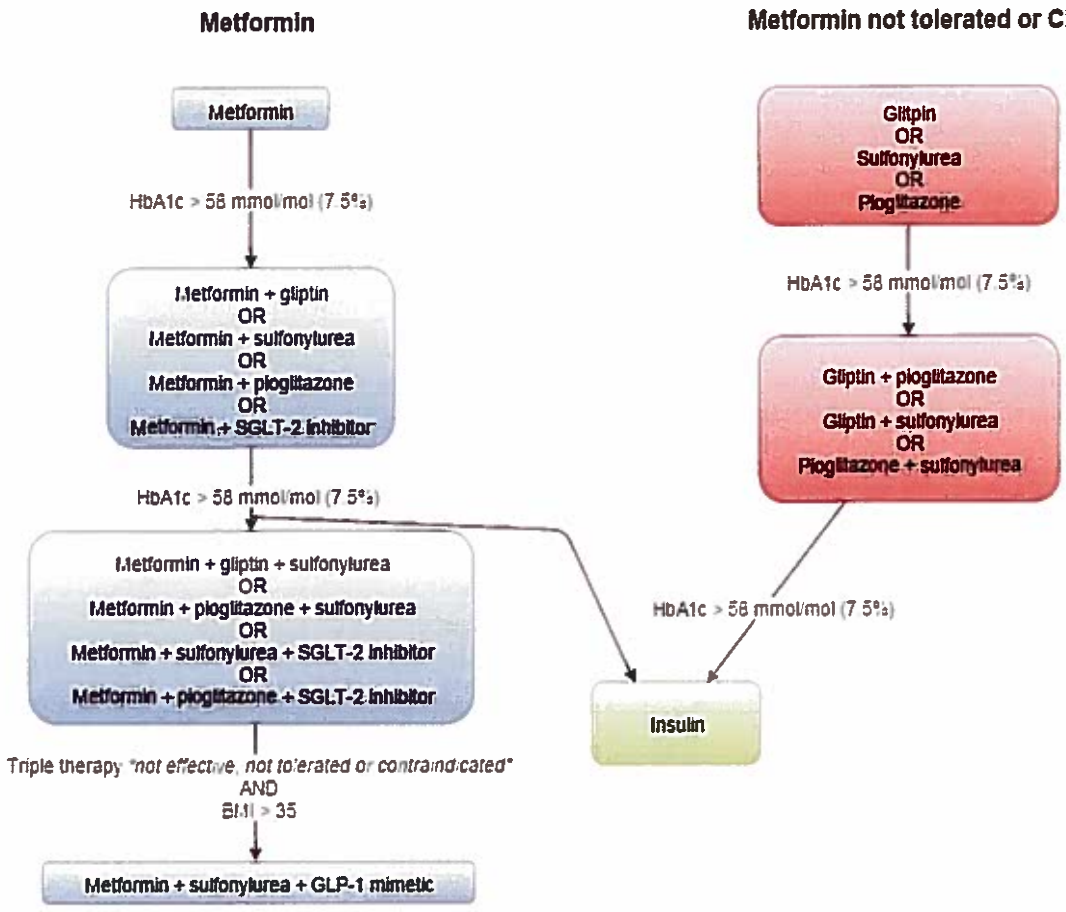
- **Usually commenced if HbA1c > 7.5%.**
- NICE recommend starting with **human NPH insulin** (**isophane**, intermediate acting) taken **at bed-time** or **twice daily** according to need.

- The appropriate recommended starting dose for intermediate acting insulin is **0.2 U/kg** or **a flat dose of 10 U**.
- A **titration** schedule based on fasting glucose levels is then recommended, with **an increase of 2 U of insulin every 3 days** until fasting glucose is in the target range of 3.9-7.2 mmol/L.
- If the fasting plasma glucose is more than 10 mmol/L, then a more aggressive up titration schedule of 4 U every 3 days can be considered.
- **Insulin glargine (Lantus®):** is a long-acting insulin analogue, it is an amalgam of Glycine and Arginine: **Glycine** is at chain A position **A21** and **two Arginines** are added to B chain position **B30**.
- Glargine and Detemir are insulin analogues, as such they are considered by NICE to be **only** suitable in cases:
  1. **Nocturnal hypoglycaemia** is a problem on isophane (NPH) insulin
  2. **Morning hyperglycaemia** on isophane (NPH) insulin results in difficult day-time blood glucose control
  3. Rapid-acting insulin analogues are used for meal-time blood glucose control.

### Special considerations

- If the patient is at risk from hypoglycaemia (or the consequences of) then a DPP-4 inhibitor or thiazolidinedione should be considered rather than a sulfonylurea
- Meglitinides (insulin secretagogues) should be considered for patients with an erratic lifestyle
- **You can consider using sitagliptin or a thiazolidinedione instead of insulin if there would be employment (eg: truck driver), social, recreational, or personal issues.**
- In patients with diabetes starting thyroxine, doses of antidiabetic drugs including insulin ma need to be increased.

**Diabetes associated with pancreatitis** is due to damage to the endocrine pancreas and associated lack of insulin. the patient's presentation: thin, with symptoms of insulinopaenia. As such, **exoenous insulin re lacement is the onl a ro riate intervention**




**EX**: the most appropriate initial insulin regime for young patient after being diagnosed with new onset Type1 DM >>> **Meal time Actrapid and insulatard at night.**

## Risk factor modification

### Hypertension

- **blood pressure targets are the same as for patients without type 2 diabetes** (see table below)
- ACE inhibitors or angiotensin II receptor blockers (ARB) are first-line
  - an ARB is preferred if the patient has a black African or African–Caribbean family origin

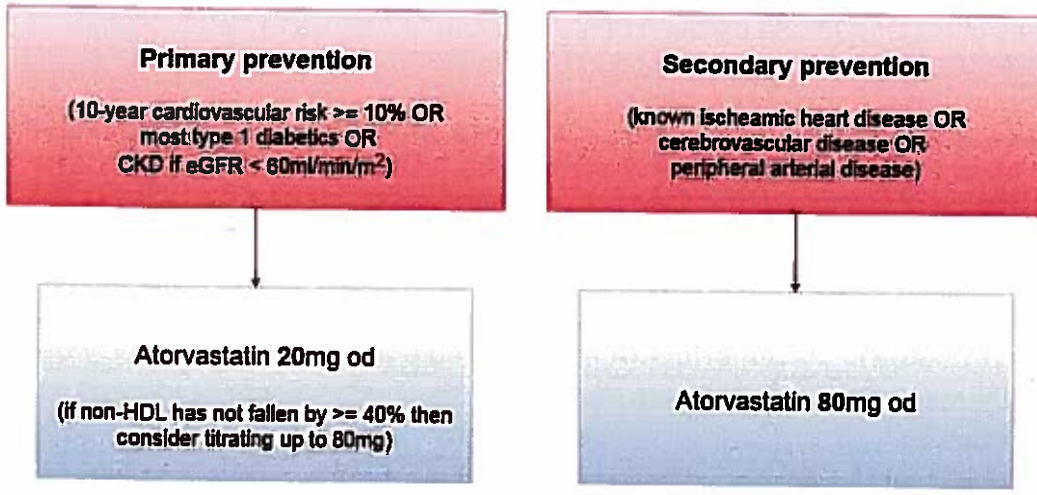
| | Clinic BP | ABPM / HBPM |
|---|---|---|
| **Age < 80 years** | 140/90 mmHg | 135/85 mmHg |
| **Age > 80 years** | 150/90 mmHg | 145/85 mmHg |

**Antiplatelets:** should not be offered unless a patient has existing cardiovascular disease

**Lipids**

- following the 2014 NICE lipid modification guidelines only patients with a 10-year cardiovascular risk > 10% (using QRISK2) should be offered a statin. The first-line statin of choice is atorvastatin 20mg on

Graphic showing choice of statin.




## Other risk factor modification:

- Current NICE guidelines suggest giving **aspirin to all patients > 50 years** and **to younger patients with other significant risk factors.** However, recent evidence does not support this approach. The 2010 SIGN guidelines do not advocate the use of aspirin for primary prevention in diabetics.
- The management of blood lipids in T2DM has changed slightly. **Previously,** all patients with T2DM > 40-years-old were prescribed statins. **Now,** patients > 40-years-old who have no obvious cardiovascular risk (e.g. Non-smoker, not obese, normotensive etc.) and have a 10 years cardiovascular risk < 20% do not need to be given a statin.
- If serum cholesterol target not reach consider **increasing simvastatin to 80mg once daily.**
- If target still not reached consider **using a more effective statin (e.g. Atorvastatin) or adding ezetimibe.**
- Target total cholesterol is **< 4.0** mmol/l
- High **triglycerides** and **HDL**-cholesterol are the commonest lipid abnormality seen in **type 2 DM**, and both are associated **with increased cardiovascular risk.**

- In total, **triglycerides above 1.7** are thought to be **associated with a 30% increase in relative cardiovascular risk.**

The **secondary** prevention: **target** of: total cholesterol to be **<4** mmol/L, **LDL** to be **<2.0** mmol/L and of **triglycerides** to the **1.7** mmol/L.

Cross-sectional studies across the **Caucasian** population have suggested that **triglyceride/HDL ratio** is **most predictive** of **insulin resistance.**
As such TG/HDL can be used to stratify both future risk of the development of CV disease and future risk of DM.
**Weight loss** and **exercise** training is seen to impact on TG/HDL ratio; **metformin** and **pioglitazone** which impact on insulin resistance both lead to modest decrease in TG and an increases in HDL in some patients.

**When is the first time that $HbA_{1c}$ is likely to be accurate post blood transfusion?** **>> 3 months**

**exam: What is the minimum time period after which the HbA1c should be repeated?** **>> 3 months** (A more accurate answer would probably be 2 months but this is not given as an option)

**exam: A Fasting glucose of one patient is = 7.7 mmol/l, but his HA1c is = 31 mmol/mol (5.0%). Which would explain the discrepancy between the HbA1c and fasting glucose levels?**
**>> Sickle-cell anaemia**

## Glycaemic index

The glycaemic index (GI) describes the **capacity of a food to raise blood glucose compared with glucose in normal glucose-tolerant individuals.**

**The risk of Foods** with a high GI:

- may be associated with an increased risk of obesity
- post-prandial hyperglycaemia associated with such foods may also increase the risk of type 2 diabetes mellitus.

The glycaemic index is shown in brackets. Glucose, by definition, would have a glycaemic index of 100

| Classification | Examples |
|---|---|
| High GI | White rice (87), baked potato (85), white bread (70) |
| Medium GI | Couscous (65), boiled new potato (62), digestive biscuit (59), brown rice (58) |
| Low GI | Fruit and vegetables, peanuts |

# Metformin

Metformin is a **biguanide** used mainly in the treatment of type 2 DM.

It has a number of actions which improves glucose tolerance (see below).

It acts to improve insulin sensitivity through mechanisms that decrease hepatic gluconeogenesis and improved muscle glucose utilization, thus some insulin must be produced for it to have an effect.

Unlike sulphonylureas **it does not cause hypoglycemia and weight gain** and is therefore **first-line,** particularly if the patient is overweight.

Metformin is also used in polycystic ovarian syndrome **(PCO)** and non-alcoholic fatty liver disease **(NASH).**

## Mechanism of action:

- **Increases insulin sensitivity (is an insulin sensitizer).**
- **Decreases hepatic gluconeogenesis.**
- May also reduce gastrointestinal absorption of carbohydrates.

## Adverse effects:

- Gastrointestinal upsets are common (nausea, anorexia, **diarrhoea**), **intolerable in 20%.**
- **Reduced vitamin B12 absorption** - rarely a clinical problem, but pateints receiving or planned to receive this drug for 3 years should receive vit. b12 supplement.
- Lactic acidosis with severe liver disease or renal failure.

**High** dose **(> 2 gm daily)** interferes with enterohepatic circulation of the bile salts **(Bile salt malabsorption) >> diarrhoea.**

Long term treatment with metformin increases the risk of vitamin B12 deficiency. The possibility of **metformin-associated B12 deficiency** should be considered in patients on metformin who suffer cognitive impairment, peripheral neuropathy, SCD of the cord or anaemia.

## Contraindications:

- It is contraindicated in subjects with **renal failure**, **hepatic failure** and **heart failure** due to the association with **lactic acidosis.**
- Chronic kidney disease (CKD): NICE recommend reviewing metformin if the creatinine is > 130 µmol/l and **stopping** metformin if creatinine **> 150** µmol/l or the **eGFR is less than 30 ml/min**/1.73m2.

- Do **not** use during suspected episodes of tissue hypoxia (e.g. **Recent MI, sepsis).**
- In the BNF, metformin in is listed as contraindicated **within 6 weeks of MI.**
- **Alcohol abuse is a relative contraindication.**
- **Stop 2 days before general anesthesia**_, restart when renal function normal.
- **Stop prior to IV contrast** e.g. angiography, restart when renal function normal.

**NB**: It is now increasingly recognized that lactic acidosis secondary to metformin is rare, although it remains important in the context of exams.

**NB**: Metformin is now sometimes used in pregnancy, for example in women with polycystic ovarian syndrome.

**NB**: Metformin may be continued (or initiated) with an eGFR less than 60 mL/min/1.73 m2, but renal function should be monitored closely (every 3-6 months). The drug should be **stopped once eGFR** falls to **less than 30 mL/min/1.73 m2 (creatinine more than 150 µmol/L).**

| |
|---|
| **N.B:** Gastrointestinal side-effects are more likely to occur if metformin is not slowly titrated up. The BNF advises **leaving at least 1 week before increasing the dose.** |
| If the patient is intolerant to standard metformin, then **modified release preparations** should be tried. |
| **N.B:** The most appropriate prescription is:<br>R/ Metformin 500mg OD with food for 14 days, then metformin 500mg bid for 14 days then review. |

## Sulfonylureas (SU)

Sulfonylureas are oral hypoglycemic drugs used in the management of T2DM.

They work by **increasing pancreatic insulin secretion (insulin secretagogues)**; and hence are only effective if functional B-cells are present.

On a molecular level they **bind to an ATP-dependent K+ ($K_{ATP}$) channel** on the cell membrane of pancreatic beta cells.

### Common adverse effects:

- **Hypoglycaemic episodes** (more common with long acting preparations such as chlorpropamide)
- **Weight gain.**

## Rarer adverse effects:

- **SIADH** (syndrome of inappropriate ADH secretion).
- **Bone marrow suppression.**
- Liver damage (**cholestatic**).
- Photosensitivity
- Peripheral neuropathy
- Sulphonylureas are a class of drugs associated with increased risk of RBCs oxidation and the absence of **G6PD** leads to **haemolytic anaemia.**
- **Sulfonylureas should be avoided in pregnancy and breast feeding.**

## Contraindications

- Pregnancy and breast feeding
- Severe cardiovascular comorbidity
- Severe liver and kidney failure
- Obesity
- Beta blockers (can mask hypoglycemic symptoms while lowering serum glucose levels)

**The combination of beta-blockers and hypoglycemia should be avoided:**

- Beta-blockers may mask the warning signs of hypoglycemia (e.g., tachycardia) and decrease serum glucose levels even further.

Sulphonylurea provide microvascular benefits, but **NO benefit was demonstrated for macrovascular outcomes** (cardiovascular disease) , in contrast to metformin.

**Sulphonylurea overdoses:**
In **sulphonylurea overdoses**, if the patient remains **hypoglycaemic despite infusion of sufficient glucose,** consider administration of **octreotide** (a somatostatin analogue which lowers insulin levels and thus raised blood glucose)

**EX:** A 62-year-old Caribbean man with new onset type 2 DM presents to the ER. He has increasing lethargy and tiredness since starting a sulphonylurea a few days earlier.
On examination he has jaundiced sclerae, his BP is 135/72 mmHg, and pulse is 95. His mucous membranes look a little pale.
Lab: Hb=10, Bilirubin = 80 µmol/L (N <17), Heinz bodies in peripheral film.
The most likely diagnosis is **Glucose-6-phosphate dehydrogenase (G6PD) deficiency.**

## Meglitinides

Meglitinides - stimulate insulin release - good for erratic lifestyle

**Meglitinides (nateglinide and repaglinide) >> increase postprandial insulin release specifically**

**Action >> closure of the p-cell K+-ATP channel.**

- Short-acting insulin secretagogues
- Blockage of ATP-sensitive potassium (KATP) channels of the pancreatic beta cells >> depolarization of the cell membrane >> calcium influx >> insulin secretion
- Act like sulfonylureas but have a weaker binding affinity and faster dissociation from the SUR1 binding site of the pancreatic channel.

**Indications:** useful for post-prandial hyperglycaemia or an **erratic eating schedule**, as patients take them shortly before meals

**Advantages**

- The shorter action of duration appears to result in less weight gain compared to traditional sulphonylureas.
- Nateglinide is more expensive than sulphonylureas but offers advantages **for shift workers and patients who tend to fast for a period of time** because doses can be skipped when meals are missed. In these patient groups there may be a lower incidence of hyperglycaemia.
- Repaglinide can be used even in CKD stages 4 and 5 without dose reduction.

**Adverse effects:** weight gain and hypoglycaemia (less so than sulfonylureas)

## Thiazolidinediones (TZD)

Thiazolidinediones are a new class of agents used in the ttt of type 2 DM.

They are **PPAR-gamma receptor agonists** and reduce peripheral insulin resistance.

The **Peroxisome Proliferator-Activated Receptor Gamma** (PPAR-gamma receptor) is an intracellular nuclear receptor. Its natural ligands are free fatty acids and it is thought to control adipocyte differentiation and function. i.e it is **activated** by **free fatty acids** and the **TZD** such as pioglitazone.

It is an **insulin sensitizer**. It upregulates genes for enzymes which deal with the metabolism of free fatty acids. These lead to **increased peripheral insulin sensitivity**, and improve glucose uptake.

Pioglitazone is not associated with hypoglycemia.

It reduces HbA1c by between 1 and 1.3%.

Rosiglitazone was withdrawn in 2010 following concerns about the cardiovascular side-effect profile.

### Adverse effects:

- **Weight gain.**
- **Fluid retention** (in around 10% of patients) - therefore contraindicated in heart failure. The risk of fluid retention is increased if the patient also takes insulin.
- **Liver** impairment: monitor LFTs.
- Recent studies have indicated an increased risk of fractures as it decrease bone mineral density.
- **Bladder cancer:** recent studies have showed an increased risk of **bladder cancer** in patients taking pioglitazone (hazard ratio 2.64).

NICE guidance on thiazolidinediones: Only continue if there is a reduction of > 0.5 percentage points in HbA1c in 6 months.

## Insulin

### Insulin: Basics

#### Secretion

- Insulin is stored in secretory granules
- Released by beta cells **as a result of increased intracellular calcium.**
- **Released in pulses about every 9-13 minutes.**
  - **This pulsing release mechanism** is important because it is thought that this keeps cells sensitive to insulin.
  - **this is one of the first things that disappears when insulin sensitivity disappears.**
- **Secreted in response to hyperglycaemia**

#### C-peptide

- a protein cleaved from proinsulin when it is activated.
- has a longer half-life than insulin, and thus is a useful measure of insulin secretion (it is more accurate than measuring insulin itself).
- The level of this can be measured in the urine.

**Insulin and C peptide are j in insulinoma and sulfonylurea use, whereas exogenous insulin lacks C- e tide.**

## Insulin therapy

### Insulin types

#### Rapid-acting insulin analogues (Aspart, Lispro, Glulisine)

- Onset: 5 mins
- Peak: 1 hour
- Duration: 3-5 hours
- **Reduces the chance of between-meal hypoglycaemia.**
- Useful for **reducing postprandial hypoglycaemia** because their profile is more in keeping with physiological insulin release.
- If there is a pre-lunch **hyperglycaemia,** that means there is a significant post- breakfast peak in glucose levels. As such, **the best management >> breakfast time injection of rapid acting insulin.**

#### Short-acting insulins (Actrapid, Humulin S)

- Onset: 30 mins
- Peak: 3 hours
- Duration: 6-8 hours
- may be used as the bolus dose in 'basal-bolus' regimes
- "Standard insulin" for lowering blood glucose levels **in an acute setting**
- **Intravenous therapy available**

#### Intermediate-acting insulins (Isophane [NPH])

- Onset: 2 hours
- Peak: 5-8 hours
- Duration: 12-18 hours
- NICE guidelines advise that, in general, a **humane isophane insulin is the first- line recommended insulin in type 2 diabetic.**

#### Long-acting insulins (Determir, Glargine)

- Onset: 1-2 hours
- Peak: **Flat profile**
- Duration: Up to 24 hours
- The main advantage > > **Reduced nocturnal hypoglycaemia**
- might be useful in someone who struggles to inject a twice a day NPH insulin to reduce the frequency of injections to once a day (e.g. someone who requires assistance to inject from a career or district nurse).
- suitable for providing a basal level of insulin which attempts to mimic the normal physiological state.

- **In which situations does insulin glargine have the clearest advantage over isophane?**
  - **In patients with type-1 diabetes who have significant nocturnal hypoglycaemia on isophane**
- NICE only recommends use of insulin glargine in patients who have **significant hypoglycaemia on isophane insulin**
- **Detemir is the only long-acting insulin that is soluble in the bottle as well as under the skin, possibly allowing for more consistent absorption.**
- **Detemir can be administered with other forms of insulin, unlike insulin glargine, which cannot be mixed with other insulins or IV fluids due to its acid vehicle.**
- **Degludec** a long-acting insulin.
  - Onset: ~1 hour
  - Half-life elimination: ~25 hours (has the highest half-life)
  - Time to peak: 9 hours

Rapid-acting insulins are your favorite GAL (Glulisine, Aspart, Lispro).

**Degludec**

- A patient with recurrent admissions for OKA secondary to missing doses can be started on degludec to reduce readmission rate.
- Oegludec has a much higher half-life than Oetemir and therefore maintains a basal insulin level when the patient omits or forgets doses. This can prevent OKA.

**Intravenous insulin is the optimal management of high blood sugar in acute myocardial infarction.**

## Insulin prescription

### Starting dose

- The guidelines recommend starting with either morning or evening long-acting insulin, or with **bedtime intermediate acting insulin.**
- **0.2 U/kg or a flat dose of 10 U is the recommended starting dose for intermediate acting insulin.**

### Targets

- Fasting and pre-prandial glucose levels >> 4-7 mmol/L.
- Post-prandial glucose levels: less than 10 mmol/L.
- In hospitalised patients the Joint British Diabetes Societies for Inpatient care (JBDS) suggest a **target** blood glucose of **6-10mmol/L**

## Monitoring

- **If patients are not using insulin, sulphonylureas or glinides (repaglinide or netaglinide), then the ADA/EASD consensus does not recommend self- monitoring of blood glucose levels.**
- Once daily long-acting insulin taken at night is monitored using pre-breakfast fasting glucose measurements. If fasting levels are in range yet the $HbA_1c$ is elevated, post- prandial monitoring is recommended.

## Dose adjustment

- Pre-prandial glucose: Mainly affected by the basal insulin dose
- Postprandial glucose is mainly affected by meal intake and prandial insulin dose.
- At least three consecutive, self-monitored fasting glucose readings should be used to adjust doses (i.e. three days minimum between dose adjustments).
- Up-titration
  - increase 2 U of insulin every three days until fasting glucose is in the target range of 3.9-7.2 mmol/L. If the fasting plasma glucose is >10 mmol/L, >> uptitration schedule of 4 U every three days can be used.
- Down-titration
  - Reduce insulin dose in steps of **20%** if hypoglycaemia occurs.

## Insulin in renal failure

- The dose of exogenous insulin is reduced 25% when eGFR is 10-50 ml/min and 50% when eGFR is < 10 ml/min

the most appropriate initial insulin regime for young patient after being diagnosed with new onset T pe1 DM >> Meal time Actrapid and insulatard at night.

## Mixtard- associated nocturnal hypoglycemia

- **This is because the insulatard component of the Mixtard peaks about 6 h after it has been given. This, along with some residual actrapid activity, gives an excess of insulin in the middle of the night, leading hypoglycaemia.**
- **Split evening insulin so take actrapid before evening meal and insulatard before bedtime**

**Hypoglycaemic episodes which occur during the day in a patient takes a basal bolus insulin regime of long-acting insulin (Insulatard®) and short- acting insulin (Actrapid®) with each meal:**

- the most appropriate next step >> Refer for **D**ose **A**djustment **F**or **N**ormal **E**ating education **(DAFNE)**
- the next step after DAFNE, should hypos persist, would be **continuous glucose monitoring**, to learn more about fluctuations in serum blood glucose over the course of the day.

those patients who have problems with **nocturnal hypoglycaemia** >> changing insulatard to insulin glargine

What is the most appropriate initial advice with respect to adjusting prandial insulin dose? **>> 1 unit of insulin er 10 grams of dieta carbohydrate**

## Diabetes Mellitus: GLP-1 and the new drugs

A number of new drugs to treat diabetes mellitus have become available in recent years. Much research has focused around the role of **glucagon-like peptide-1 (GLP-1)**, a **hormone** released by **the small intestine in response to an oral glucose load.**

Whilst it is well known that insulin resistance and insufficient B-cell compensation occur other effects are also seen in (T2DM).

In normal physiology an **oral** glucose load results in a **greater release of insulin** than if the same load is given intravenously - this known as the **"incretin effect"**. This effect is **largely mediated by GLP-1** and is known to be **decreased in T2DM.**

Increasing GLP-1 levels, either by the administration of an analogue or inhibiting its breakdown, is therefore the target of two recent classes of drug.

### Glucagon-like peptide-1 (GLP-1) mimetics (e.g. Exenatide or Liraglutide):

- Increase insulin secretion
- Inhibit glucagon secretion by the liver
- It suppresses appetite and slow gastric emptying
- It does **not increase insulin sensitivity**
- licensed for use in T2DM
- Must be given by **subcutaneous** injection **within 60 minutes before the morning and evening meals. It should not be given after a meal.**
- Patient has **no** need to **self-monitor** his blood glucoses by **glucometer.**
- May be combined with metformin, a sulfonylurea or a thiazolidinedione.
- Typically results in **weight loss.**

- It is a good choice in patients who are significantly overweight.
- Major adverse effect is **nausea** and **vomiting.**

## NICE guidelines on the use of Exenatide / Liraglutide:

Exenatide is an example of a **glucagon-like peptide-1 (GLP-1) mimetic.** These drugs increase insulin secretion and inhibit glucagon secretion. One of the major advances of GLP-1 mimetics is that they typically result in weight loss, in contrast to many medications such as insulin, sulfonylureas and thiazolidinediones. They are sometimes used in combination with insulin in T2DM to minimise weight gain.

Exenatide must be given by subcutaneous injection within 60 minutes before the morning and evening meals. It should not be given after a meal. Liraglutide is the other GLP-1 mimetic currently available. One the main advantages of liraglutide over exenatide is that it only needs to be given once a day.

Both exenatide and liraglutide may be combined with metformin and a sulfonylurea. Standard release exenatide is also licensed to be used with basal insulin alone or with metformin. Please see the BNF for a more complete list of licensed indications.

**NICE state the following:**

*Consider adding exenatide to metformin and a sulfonylurea if:*

- *BMI >= 35 kg/m² in people of European descent and there are problems associated with high weight, or*
- *BMI < 35 kg/m² and insulin is unacceptable because of occupational implications or weight loss would benefit other comorbidities.*

NICE like patients to have achieved a > 11 mmol/mol (1%) reduction in HbA1c and 3% weight loss after 6 months to justify the ongoing prescription of GLP-1 mimetics.

The major adverse effect of GLP-1 mimetics is **nausea and vomiting.** The Medicines and Healthcare products Regulatory Agency has issued specific warnings on the use of exenatide, reporting that is has been linked to severe pancreatitis in some patients.

## Dipeptidyl peptidase-4 (DPP-4) inhibitors (e.g. Vildagliptin, Sitagliptin):

- **Oral** preparation.
- Trials to date show that the drugs are **relatively well tolerated** with **no increased incidence of hypoglycemia.**
- **Do not cause weight gain.**
- SE: **GIT disturbance**: nausea, flatulence, diarrhea and constipation.

## NICE guidelines on DPP-4 inhibitors:

- Continue DPP-4 inhibitor only if there is a reduction of > 0.5 percentage points in HBA1c in 6 months.
- NICE suggest that a DPP-4 inhibitor might be preferable to a thiazolidinedione if further weight gain would cause significant problems, a thiazolidinedione is contraindicated or the person has had a poor response to a thiazolidinedione.

# Sodium-glucose cotransporter 2 inhibitors (gliflozins)

**Empagliflozin has been shown to reduce cardiovascular mortality**

**Examples:** Include **canagliflozin, dapagliflozin** and **empagliflozin**

**Mechanism of action:** reversible inhibition of SGLT-2 in the proximal convoluted tubule of the kidney >> ↓ glucose reabsorption >> glycosuria and polyuria.

## Indications

- Empagliflozin or canagliflozin may play a role in patients with overt cardiovascular diseases (CVD) or heart failure not reaching glycemic goals with metformin and lifestyle modifications
- may have a role **as a third agent in those who cannot or will not take insulin**, when full doses of metformin and a sulfonylurea have not produced satisfactory metabolic control, or **in patients in whom risk of hypoglycemia is high** (frail, older adults) or **in whom avoidance of weight gain is a priority.**

## Advantages

- Glycemic efficacy: lowers HbA1c by 0.6% over 3 months
- **Promotes weight loss** (modest calorie spillage into the urine)
  - **there for it is better than gliptins in obese patient who does not achieve control by metformin**
- ↓ Blood pressure (**Sodium loss >> fall in BP**)
- ↓ Risk of cardiovascular mortality in patients with type 2 OM and cardiovascular disease
- Reduce uric acid, which may over the longer term reduce nephropathy progression
- Do not usually cause hypoglycemia

## Adverse effects

- **Recurrent infections** due to glucosuria
  - **Recurrent urinary infections** ( ↑ glucose in the urine (Glycosuria) >> predispose to bacterial growth)

  - Genital infection (Vulvovaginal candidiasis): **contra-indicated in patients with recurrent thrush.**
  - Necrotizing fasciitis of the perineum
- **Diabetic ketoacidosis (patients may present with euglycaemic ketoacidosis)**
  - SGLT-2 inhibitors >> ↑ **glucagon,** >> ↑ lipid oxidation >>↑ risk of ketoacidosis
- **Increased risk of bone fracture**
  - SGLT-2 inhibitors >> ↑ **PTH** >> ↑ tbone turnover >> ↑ risk of bone fracture.
  - SGLT-2 inhibitors >> ↑ fibroblast growth factor (FGF-23) >> ↓ vitamin D >> ↓ bone mineralisation.
- Acute kidney injury
- Dehydration >> weight loss, orthostatic hypotension
- **Increased total cholesterol,** (both HDL and LDL)
- ↑ Risk of lower limb amputation: Empagliflozin is preferred rather than canagliflozin. Canagliflozin found to be associated with increased risk of lower limb amputation and fractures.

### Contraindications

- Renal Impairment: **eGFR <30 ml/minute/1.73 m2: Use is** contraindicated.
- Recurrent urinary tract infections (e.g., in patients with anatomical or functional anomalies of the urinary tract)

## Alpha-glucosidase inhibitors

### Overview

- These are **acarbose, miglitol** and voglibose.
- Not usually used as first-line therapy, because of modest efficacy and poor tolerance.

**Mechanism of action:** inhibit the upper gastrointestinal enzymes (alpha-glucosidases) that convert complex polysaccharide carbohydrates into monosaccharides and thereby slow absorption of glucose and reduce postprandial blood glucose concentration.

### Advantages

- They may be used as part of a combination regimen in people who consume high- carbohydrate diets and have high postprandial glucose levels.
- reduction in risk of new onset type 2 diabetes and **cardiovascular events.**

## Side effects

- Abdominal pain, flatulence and diarrhea (Using glucosidase inhibitors is like making a person lactose intolerant).
  - Mechanism of diarrhoea: Alpha-glucosidase inhibitors >> block glucose absorption >> the sugar remains in the bowel >> bacteria eat the glucose, and cast off gas and acid.

# Diabetes mellitus: Ramadan

We know that type 2 diabetes mellitus is more common in people of Asian ethnicity and a significant proportion of those patients in the UK will be Muslim. The BMJ published an excellent and comprehensive review of this issue in 2010[1].
It is important that we can give appropriate advice to Muslim patients to allow them safely observe their fast. This is particularly important from 2014 as Ramadan is due to fall in the long days of the summer months for several years henceforth.

Clearly it is a personal decision whether a patient decides to fast. It may however be worthwhile exploring the fact that people with chronic conditions are exempt from fasting or may be able to delay fasting to the shorter days of the winter months. It is however known that many Muslim patients with diabetes do not class themselves as having a chronic/serious condition which should exempt them from fasting. Around 79% of Muslim patients with type 2 diabetes mellitus fast Ramadan[2].There is an excellent patient information leaflet from Diabetes UK and the Muslim Council of Britain which explores these options in more detail.

**If a patient with type 2 diabetes mellitus does decide to fast:**

- they should try and and eat a meal containing long-acting carbohydrates prior to sunrise (Suhoor).
- patients should be given a blood glucose monitor to allow them to check their glucose levels, particularly if they feel unwell
- for patients taking metformin the expert consensus is that the dose should be split **one-third before sunrise** (Suhoor) and **two-thirds after sunset** (Iftar).
- expert consensus also recommends switching once-daily sulfonylureas to after sunset. For patients taking twice-daily preparations such as gliclazide it is recommended that a larger proportion of the dose is taken after after sunset
- no adjustment is needed for patients taking pioglitazone

Management of people with diabetes wanting to fast during Ramadan BMJ
2. Salti I et al. Results of the Epidemiology of Diabetes and Ramadan (EPIDIAR) study. Diabetes Care

## Latent autoimmune diabetes of adulthood (LADA)

**Definition:** a variant of diabetes characterized by a late onset of type 1 (autoimmune) diabetes that is often mistaken for type 2 diabetes.

**Epidemiology:** constitutes approximately 10% of patients incorrectly labelled as type 2 diabetic.

**Feature**

- **Features consistent with type 1 diabetes (eg: weight loss)**
- In contrast to type 2 diabetes, patients are typically younger and without an increased body habitus.
- In contrast to type 1 diabetes, insulin is not usually required in the early stages of the disease. the progression of autoimmune -cell failure is slow.

**Diagnosis:** Glutamic Acid Decarboxylase (GAD) Autoantibodies test

**Management**

- early use of insulin may prolong beta-cell function
- a recent Cochrane review concluded that a **sulphonylurea should not be the first line treatment** since it may be **associated with a more rapid progression to insulin dependence**

## MODY (Type 1.5 DM)

Maturity-onset diabetes of the young (MODY) is characterized by the development of **type 2 diabetes mellitus** in **patients < 25 years old.**

It accounts for 1-2% of diabetes cases, and is an important diagnosis as the therapy may be different compared with T1DM and T2DM.

It is sometimes called **type 1.5 DM.**

It is typically inherited as an **autosomal dominant** condition (i.e. There is usually a **strong family history).**

Over 6 different genetic mutations have been identified as leading to MODY.

**Ketosis is not a feature at presentation.**

**Treatment:** **One** third of patients require insulin therapy and around **one** third may be controlled with oral hypoglycaemic drugs.
**Sulphonylureas (SUs)** would be the initial drug of choice, because at least for the first few years, capacity to secrete insulin is preserved, and use of SUs restores insulin release, avoiding the need for insulin therapy.

MODY >>> Autosomal Dominant

**MODY 1:**
- < 10%
- Due to defect in **HNF-4 alpha gene** (Hepatocyte Nuclear Factor).

**MODY 2:**
- 20% of cases.
- Due to a defect in the **glucokinase gene.**
- 90% of MODY 2 are controlled on diet therapy alone.

**MODY 3:**
- **60**% of cases (**most common**).
- Due to a defect in the **HNF-1 alpha gene**

**MODY 5**
- rare
- due to a defect in the HNF-1 beta gene
- liver and renal cysts

**EX:** Male pt. 18 yrs. old with recurrent episodes of penile thrush with positive family history of T2DM, FBS checked twice 8.1 and 8.2 mmol/l with HbA1C 8.9% >>> **MODY type 3** >>> Initial ttt **Sulfonylureas**.

## Diabetic ketoacidosis (DKA)

**Approximately 25% of patients with type 1 DM will first present in DKA** although often there are symptoms such as thirst, polyuria and weight loss which have been ignored.
The most common precipitating factors of diabetic ketoacidosis (DKA) are infection, missed insulin doses and myocardial infarction.

The **low insulin level** in DKA >> stimulate **lipolysis** >> production of ketone bodies, β-hydroxybutyrate and acetoacetate, which can be used as a metabolic fuel.

### Features
- abdominal pain
- polyuria, polydipsia, dehydration
- Kussmaul respiration (deep hyperventilation)
- Acetone-smelling breath ('pear drops' smell)

- **serum sodium is falsely low** due to the osmotic load of glucose.
- Blood count:
  - **Platelet secretory activity** is often **increased** in OKA, but **aggregation decreased**.
  - **Neutrophil** count is also commonly raised and correlates with ketone body levels, so does not necessarily imply underlying infection.

## Diagnostic criteria

| American Diabetes Association | Joint British Diabetes Societies |
|---|---|
| **Key points**<br>• glucose > 13.8 mmol/l<br>• pH < 7.30<br>• serum bicarbonate <18 mmol/l<br>• anion gap > 10<br>• ketonaemia | **Key points**<br>• glucose > 11 mmol/l or known diabetes mellitus<br>• pH < 7.3<br>• bicarbonate < 15 mmol/l<br>• ketones > 3 mmol/l or urine ketones ++ on dipstick |

A **raised amylase** in the **absence** of frank pancreatitis is common in patients with DKA, indeed many patients complain of a degree of abdominal pain at the time of presentation. **No** specific management is required and amylase falls with rehydration and control of blood glucose.

## Management:

- **Fluid** replacement: most patients with DKA are deplete around **5-8 liters**. **Isotonic saline** is used initially.
- **Insulin**: an intravenous infusion should be **started at 0.1 unit/kg/hour**. Once blood glucose is < 15 mmol/l an infusion of 5% dextrose should be started.
- **correction of electrolyte disturbance**
  - serum potassium is often high on admission despite total body potassium being low
  - this often falls quickly following treatment with insulin resulting in hypokalaemia
  - potassium may therefore need to be added to the replacement fluids
  - if the rate of potassium infusion is greater than 20 mmol/hour then cardiac monitoring may be required
- **long-acting insulin** should be continued, **short-acting insulin** should be stopped
- **LMWH** to prevent DVT.

### JBDS example of fluid replacement regime for patient with a systolic BP on admission 90mmHg and over

| Fluid | Volume |
|---|---|
| 0.9% sodium chloride 1L | 1000ml over 1st hour |
| 0.9% sodium chloride 1L with potassium chloride | 1000ml over next 2 hours |
| 0.9% sodium chloride 1L with potassium chloride | 1000ml over next 2 hours |
| 0.9% sodium chloride 1L with potassium chloride | 1000ml over next 4 hours |
| 0.9% sodium chloride 1L with potassium chloride | 1000ml over next 4 hours |
| 0.9% sodium chloride 1L with potassium chloride | 1000ml over next 6 hours |

Please note that slower infusion may be indicated in young adults (aged 18-25 years) as they are at greater risk of cerebral oedema.

### JBDS potassium guidelines

| Potassium level in first 24 hours (mmol/L) | Potassium replacement in mmol/L of infusion solution |
|---|---|
| Over 5.5 | Nil |
| 3.5-5.5 | 40 |
| Below 3.5 | Senior review as additional potassium needs to be given |

## Resolution

### DKA resolution is defined as:

- pH >7.3 and
- blood ketones < 0.6 mmol/L and
- bicarbonate > 15.0mmol/L

### Further points

- both the ketonaemia and acidosis should have been resolved within 24 hours. If this hasn't happened the patient requires senior review from an endocrinologist
- if the above criteria are met and the patient is eating and drinking switch to subcutaneous insulin
- the patient should be reviewed by the diabetes specialist nurse prior to discharge

**The typical fluid deficit associated with DKA is approximately: 6 litres**

## Complications

Complications may occur from DKA itself or the treatment:

- gastric stasis
- thromboembolism

- arrhythmias secondary to hyperkalaemia/iatrogenic hypokalaemia
- iatrogenic due to incorrect fluid therapy: **cerebral oedema***, hypokalaemia, hypoglycaemia
- acute respiratory distress syndrome
- acute kidney injury

**(SCE- question samples.mrcpuk.org)**

A 26-year-old woman with **DKA.** After 24 hours of treatment with intravenous fluids, potassium and insulin, her normal subcutaneous insulin regimen was resumed. However, she felt nauseated and there was a concomitant increase in **blood ketones to 3.5 mmol/L** (<0.3). random plasma **glucose: 7.3 mmol/L** **What is the most appropriate next step in management?**

- Start glucose 10% with fixed-rate intravenous insulin
  - **A fixed-rate insulin infusion is recommended for faster resolution of OKA.**
  - **If the blood glucose is below 14 mmol/L, it is necessary to administer intravenous infusion of 10% glucose in order to avoid hypoglycaemia and permit the continuation of fixed-rate intravenous insulin.**

**children/young adults are particularly vulnerable to cerebral oedema** following fluid resuscitation in DKA and often need 1:1 nursing to monitor neuro-observations, headache, irritability, visual disturbance, focal neurology etc. It usually occurs 4-12 hours following commencement of treatment but can present at any time. If there is any suspicion a CT head and senior review should be sought

The mortality associated with DKA remains stubbornly around the **2-5%** since the 1970s specifically, mortality relates to **cerebral oedema.**

# Hyperosmolar Hyperglycaemic Non ketotic Coma (HHNC)

Hyperosmolar hyperglycaemic state (HHS) is a medical emergency which is extremely difficult to manage and has a significant associated mortality. Hyperglycaemia results in osmotic diuresis, severe dehydration, and electrolyte deficiencies. HHS typically presents in the elderly with type 2 diabetes mellitus (T2DM), however the incidence in younger adults is increasing. It can be the initial presentation of T2DM.

It is extremely important to differentiate HHS from diabetic ketoacidosis (DKA) as the management is different, and treatment of HHS with insulin (e.g. as part of a DKA protocol) can result in adverse outcomes.

The first 24 hours of treatment is very labour intensive so these patients are best managed in either a medical high dependency unit.

HHS has a higher mortality than DKA and may be complicated by vascular complications such as myocardial infarction, stroke or peripheral arterial thrombosis.

Seizures, cerebral oedema and central pontine myelinolysis (CPM) are uncommon but documented complications of HHS. Whilst DKA presents within hours of onset, HHS comes on over many days, and consequently the dehydration and metabolic disturbances are more extreme.

## Pathophysiology

- Hyperglycaemia results in osmotic diuresis with associated loss of sodium and potassium
- Severe volume depletion results in a significant raised serum osmolarity (typically > than 320 mosmol/kg), resulting in hyperviscosity of blood.
- Despite these severe electrolyte losses and total body volume depletion, the typical patient with HHS, may not look as dehydrated as they are, because hypertonicity leads to preservation of intravascular volume.

## Clinical features

- General: fatigue, lethargy, nausea and vomiting
- Neurological: altered level of consciousness, headaches, papilloedema, weakness
- Haematological: hyperviscosity (may result in myocardial infarctions, stroke and peripheral arterial thrombosis)
- Cardiovascular: dehydration, hypotension, tachycardia

## Diagnosis

- 1. Hypovolaemia
- 2. Marked Hyperglycaemia (>30 mmol/L) without significant ketonaemia or acidosis
- 3. Significantly raised serum osmolarity (> 320 mosmol/kg)
- Note: A precise definition of HHS does not exist, however the above 3 criteria are helpful in distinguishing between HHS and DKA. It is also important to remember that a mixed HHS / DKA picture can occur.

## Management

The goals of management of HHS can be summarised as follows:

- Normalise the osmolality (gradually)
  - the serum osmolality is the key parameter to monitor
  - if not available it can be estimated by 2 * $Na^+$ + glucose + urea
- Replace fluid and electrolyte losses
- Normalise blood glucose (gradually)

## Fluid replacement

- Fluid losses in HHS are estimated to be between 100 - 220 ml/kg (e.g. 10-22 litres in an individual weighing 100 kg).
- The rate of rehydration will be determined by assessing the combination of initial severity and any pre-existing co-morbidities (e.g. heart failure and chronic kidney disease). Caution is needed, particularly in the elderly, where too rapid rehydration may precipitate heart failure but insufficient may fail to reverse an acute kidney injury.
- Intravenous (IV) 0.9% sodium chloride solution is the first line fluid for restoring total body fluid.
- It is important to remember that isotonic 0.9% sodium chloride solution is already relatively hypotonic compared to the serum in someone with HHS. Therefore in most cases it is very effective at restoring normal serum osmolarity.
- If the serum osmolarity is not declining despite positive balance with 0.9% sodium chloride, then the fluid should be switched to 0.45% sodium chloride solution which is more hypotonic relative to the HHS patients serum osmolarity
- IV fluid replacement should aim to achieve a positive balance of 3-6 litres by 12 hours and the remaining replacement of estimated fluid losses within the next 12 hours.
- Existing guidelines encourage vigorous initial fluid replacement and this alone (without insulin) will result in a gradual decline in plasma glucose and serum osmolarity. A rapid decline is potentially harmful (see below) therefore insulin should NOT be used in the first instance unless there is significant ketonaemia or acidosis

- The aim of treatment should be to replace approximately 50% of estimated fluid loss within the first 12 hours and the remainder in the following 12 hours. However this is just a guide, and clinical judgement should be applied, particularly in patient with co-morbidities such as heart failure and chronic kidney disease (which may limit the speed of correction).

## Monitoring response to treatment

- The key parameter in managing HHS is the osmolality to which glucose and sodium are the main contributors. Rapid changes of serum osmolarity are dangerous and can result in cardiovascular collapse and central pontine myelinolysis (CPM).
- Guidelines suggest that serum osmolarity, sodium and glucose levels should be plotted on a graph to permit appreciation of the rate of change. They should be plotted hourly initially.
- Not all laboratories have readily available access to serum osmolarity measurements. If not available then a calculated osmolarity can be estimated with 2Na + glucose + urea
- Fluid replacement alone (without insulin) will gradually lower blood glucose which will reduce osmolality
- A reduction of serum osmolarity will cause a shift of water into the intracellular space. This inevitably results in a rise in serum sodium (a fall in blood glucose of 5.5 mmol/L will result in a 2.4 mmol/L rise in sodium). This is not necessarily an indication to give hypotonic solutions. If the inevitable rise in serum Na+ is much greater than 2.4 mmol/L for each 5.5 mmol/L fall in blood glucose this would suggest insufficient fluid replacement. Rising sodium is only a concern if the osmolality is NOT declining concurrently.
- Rapid changes must be avoided. A safe rate of fall of plasma glucose of between 4 and 6 mmol/hr is recommended. The rate of fall of plasma sodium should not exceed 10 mmol/L in 24 hours.
- A target blood glucose of between 10 and 15 mmol/L is a reasonable goal.
- Complete normalisation of electrolytes and osmolality may take up to 72 hours.

## Insulin

- Fluid replacement alone with 0.9% sodium chloride solution will result in a gradual decline of blood glucose and osmolarity
- Because most patients with HHS are insulin sensitive (e.g. it usually occurs in T2DM), administration of insulin can result in a rapid decline of serum glucose and thus osmolarity.

- Insulin treatment prior to adequate fluid replacement may result in cardiovascular collapse as the water moves out of the intravascular space, with a resulting decline in intravascular volume.
- A steep decline in serum osmolarity may also precipitate CPM.
- Measurement of ketones is essential for determining if insulin is required.
- If significant ketonaemia is present (3β-hydroxy butyrate is more than 1 mmol/L) this indicates relative hypoinsulinaemia and insulin should be started at time zero (e.g. mixed DKA / HHS picture). The recommended insulin dose is a fixed rate intravenous insulin infusion given at 0.05 units per kg per hour.
- If significant ketonaemia is not present (3β-hydroxy butyrate is less than 1 mmol/L) then do NOT start insulin.

### Potassium

- Patients with HHS are potassium deplete but less acidotic than those with DKA so potassium shifts are less pronounced
- Hyperkalaemia can be present with acute kidney injury
- Patients on diuretics may be profoundly hypokalaemic
- Potassium should be replaced or omitted as required

## Diabetic Neuropathy

### Peripheral neuropathy

Diabetes typically leads to sensory loss and not motor loss. Sensory loss typically results in a 'glove and stocking' distribution, with the lower legs affected first due to the length of the sensory neurons supplying this area. Painful diabetic neuropathy is also a common problem in clinical practice.

NICE updated it's guidance on the management of neuropathic pain in 2013. Diabetic neuropathy is now managed in the same way as other forms of neuropathic pain:

- first-line treatment: **amitriptyline, duloxetine, gabapentin or pregabalin**
- if the first-line drug treatment does not work try one of the other 3 drugs
- tramadol may be used as 'rescue therapy' for exacerbations of neuropathic pain
- topical capsaicin may be used for localised neuropathic pain (e.g. post-herpetic neuralgia)
- pain management clinics may be useful in patients with resistant problems

**Duloxetine** is the standard first line therapy recommended in NICE guidelines for the management of **peripheral neuropathy**. The starting dose is **60 mg daily** although this may be increased **up to 120 mg/day**. It **cannot** be used in patients with a history of **acute narrow angle glaucoma.**
**Amitriptyline** is an **alternative** option to duloxetine **if** it is contraindicated; a dose of 10-75 mg/day is recommended.

Amitriptyline SE: **urinary retention** so take care with old male with **BPH**, and again is contraindicated in **glaucoma.**

**Gabapentin** is used in the management of neuropathy, but more usually **pregabalin** is recommended either as a **second** line agent or in combination with amitriptyline.

If there is **renal impairment**, **pregabalin** is preferable over gabapentin.

Carbamazepine is not featured in the NICE guidelines for the management of peripheral neuropathy.

## Gastrointestinal autonomic neuropathy

### Gastroparesis

- symptoms include erratic blood glucose control, bloating and vomiting
- management options include metoclopramide, domperidone or erythromycin (prokinetic agents)

### Chronic diarrhoea

- often occurs at night

### Gastro-oesophageal reflux disease

- caused by decreased lower esophageal sphincter (LES) pressure

## Diabetic amyotrophy:

It is not uncommonly a presenting feature of diabetes (**T2DM**) in the **elderly**.
It is thought to be caused by the **occlusion** of the **vasa nervorum** of the proximal lumbar plexus and/or femoral nerve.
It affects the **lumbosacral plexus LMNL.**
It is often **associated with poor diabetic control**, and may improve with good control (although it often **self-resolves with time**).
The features are of an **asymmetrical** but **bilateral quadriceps wasting** and **weakness** with **diminished knee reflexes**.
It may also be associated with **marked weight loss.**
The **improved glycemic control** is the most important initial therapeutic intervention. If not be achieved by oral antidiabetic medications so **Insulin** is the most appropriate next step.

**Transition to insulin therapy** is recommended because it is likely to improve the glycemic control and may impact progression of neuropathy.

**Recovery** of diabetic amyotrophy **happens over 3-4 months, but only 50%** achieve **complete** recovery.

**EX:** Old male patient 70 years old with two month history of **weight loss** and **weakness**. He says that his symptoms started with **a severe pain**, affecting lower back and anterior thighs. It had a **burning** quality and was worse at **night**.

Examination of the lower limbs reveals a **bilateral weakness of knee extension**. He is **unable to rise from the squatting position**. There is **absence of the knee reflex** but the ankle reflexes are preserved and both plantars are flexor. There are no abnormalities on sensory examination.

EMG shows **multifocal denervation** in paraspinous & leg muscles.

May be associated with **postural hypotension** due to **diabetic autonomic neuropathy. Treatment**: bed-head elevation, support stocking, adequate intake of NaCl, fludrocortisone starting dose 50 Mcg/day up to 400 Mcg/day, avoid diuretics, vasodilators, CCBs and TCA as they may exacerbate the condition.

D.D: Osteomalacia, hyperthyroidism and Cushing's would be unlikely as the proximal myopathy involves quadriceps and hamstrings and knee reflexes would be preserved. Pain is usually not a predominant feature.

D.D: Vitamin B12 deficiency tends to initially cause peripheral neuropathy, with loss of vibration sense and position followed by areflexia and weakness. This then develops into spasticity, Babinski plantars and ataxia if left untreated.

## Adhesive capsulitis (frozen shoulder):

- limited **both active** and **passive** movements of **all** directions.
- The shoulder is **tender** to palpation.
- **Night** pain in the affected shoulder that may **interfere with sleep**.
- Pain and stiffness usually develop **gradually** over several months to a year but progress rapidly in some patients.
- It occurs more commonly in **women after age 50**.
- It is strongly associated with **DM type I** as many as **40%** of patients developing this problem at some stage.

**EX:** An 85-year-old woman with **DM** presented with **sudden onset** of **wild flinging movements** of the **left arm** which **disappeared during sleep**.

What is the most likely explanation >>> **hemiballismus**, and in diabetes is likely to be due to a **vascular event** in the **contralateral sub thalamic nucleus**.

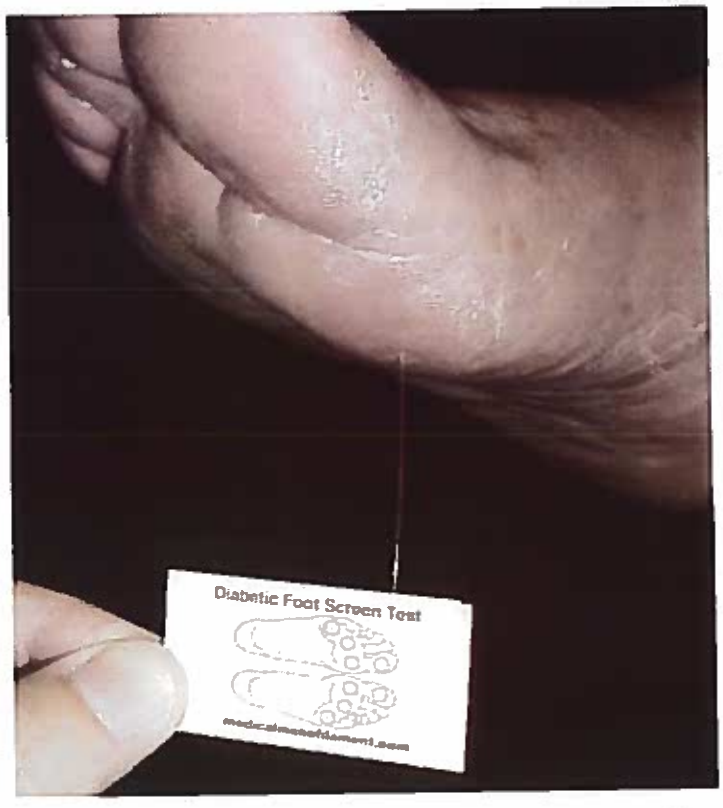
**Treatment:** Haloperidol or chlorpromazine or Topiramate.

## Diabetic foot ulceration (DFU):

- The most common pathogens are aerobic Gram positive bacteria (particularly **Staphylococcus aureus** and beta-haemolytic Streptococci).
- **Callus formation at pressure areas** is an important predictor of potential ulceration.
- **Plantar** ulceration is usually a consequence of **neuropathy** and **minor skin trauma** is probably the most common initiating event.
- **Blood flow** is often **decreased** with autonomic neuropathy hence **sympathectomy** may be performed to improve skin blood flow.
- It is **difficult radiographically** to **distinguish** between Charcot's joint and osteomyelitis.

**Diabetic foot ulcer that has occurred at the amputation**

Charcot feet bilaterally in a person with poorly controlled diabetes. Note the pronation of the feet with the abnormal bulging of the medial foot. X-rays showed abnormal tarsal bones secondary to diabetic neuropathy.




Patient with diabetes and tinea pedis being tested with a monofilament for sensation.

# Diabetic Dermopathy

Diabetic dermopathy on the lower legs that is particularly prominent over the shins

Diabetic dermopathy on the leg showing pretibial hyperpigmentation and healed ulcers with hypopigmentation. There are also signs of erythema and fine scale

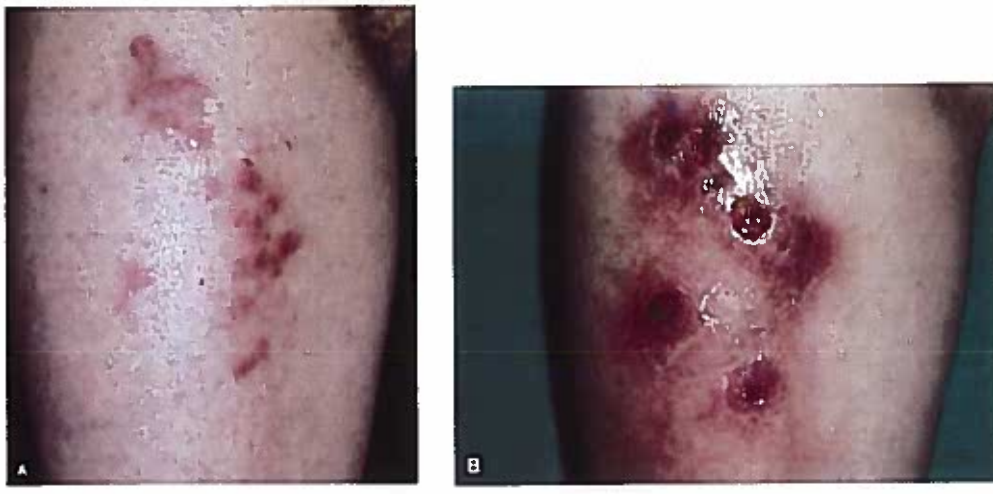
Acanthosis nigricans in a woman with type 2 diabetes and obesity. She is requesting that her skin tags be removed.

Acanthosis nigricans on the neck and in the axilla of an overweight 13-year-old Hispanic girl. She also has hirsutism, secondary amenorrhea,

Eruptive xanthomas on the extremities and trunk of a young man with untreated type 2 diabetes and hyperlipidemia.

Necrobiosis lipoidica diabeticorum on the lower leg with typical findings of skin atrophy, yellow coloration, and prominent blood vessels.

Diabetic dermopathy on both lower extremities of a middle-age man with diabetes. The sparse hair is secondary to his vasculopathy.



**A.** Necrobiosis lipoidica on the leg of a woman with no diabetes. It was biopsy proven and treated. **B.** Worsening and ulcerations of necrobiosis lipoidica despite treatment with topical steroids

## Diabetic Retinopathy

It is **the most common cause of blindness** in **adults aged 35-65 years-old**.

Diabetic retinopathy occurs in **both** type 1 and 2 DM and may be a presenting feature in type 2 as the **condition may have existed for many years prior** to diagnosis.

Progression may be slowed with **improved** both **glycemic** and **hypertensive control** but the latter has been shown to be **more** effective at reducing progression (UKPDS).

There are no data at present to suggest that statin therapy reduces disease progression.

**Hyperglycemia** is thought to cause increased retinal blood flow and abnormal metabolism in the retinal vessel walls. This precipitates damage to endothelial cells and pericytes.

**Endothelial dysfunction** leads to **increased vascular permeability** which causes the characteristic exudates seen on fundoscopy.

**Pericytes dysfunction** predisposes to the formation of **microaneurysms.**

**Neovasculization** is thought to be caused by the production of growth factors in response to retinal ischaemia.

**Despite** quite **marked** new vessel disease the **visual acuity may be normal.**

In exams you are most likely to be asked about the characteristic features of the various stages/types of diabetic retinopathy.

Recently a new classification system has been proposed, dividing patients into those with non-proliferative diabetic retinopathy (**NPDR**) and those with proliferative retinopathy (**PDR**):

| Traditional classification | New classification |
|---|---|
| Background retinopathy:<br>1) Microaneurysms **(MA) (dots)**<br>2) **Blot hemorrhages. (<=3)**<br>3) **Hard exudates (HE): collections of exudated lipid and protein**<br>4) **Seen in** both **type 1 & 2 DM**<br>Pre-proliferative retinopathy:<br>1) **Cotton wool spots (CWS): (soft exudates; ischemic infarcts of the nerve fiber layer of the retina)**<br>2) **> 3 blot hemorrhages'**<br>3) **Venous beading/looping**<br>4) **Deep/dark cluster hemorrhages**<br>5) **More common in** Type I DM, **treat with** laser **photocoagulation.** | **Mild NPDR:**<br>• 1 or more microaneurysm<br>**Moderate NPDR:**<br>• Microaneurysms<br>• Blot hemorrhages.<br>• Hard exudates<br>• Cotton wool spots,<br>• Venous beading/looping and<br>• Intraretinal microvascular abnormalities (IRMA) less severe than in severe NPDR<br>**Severe NPDR:**<br>• Blot hemorrhages and microaneurysms in 4 quadrants<br>• Venous beading in at least 2 quadrants<br>• IRMA in at least 1 quadrant |

| Prevalence | Risk factors |
|---|---|
| • 2-6% of background retinopathy.<br>• 20-60% pre-proliferative retinopathy.<br>• 70-75% of proliferative cases | • ↑HbA1C<br>• Proteinuria.<br>• Duration of DM |

## Proliferative retinopathy:

- Retinal **neovascularization** - may lead to vitrous haemorrhage
- Fibrous tissue forming anterior to retinal disc
- More common in **Type I DM**, **50% blind in 5 years**
- **Normal visual acuity** is seen in **proliferative retinopathy.**
- **Urgent** referral to **ophthalmologist** for **panretinal photocoagulation.**

## Maculopathy:

- Based on **location** rather than severity, **anything is potentially serious**
- **Hard exudates** and other 'background' changes on macula.
- Check visual acuity.
- More common in **Type II DM.**

**Microaneurysm** on **fluorescein angiography** is the **earliest** sign of **Diabetic Nephropathy.**

**Asymmetric** DM Retinopathy >>> suspect **ocular ischemia (carotid artery disease)**

**In T1DM >> Urgent** referral to an ophthalmologist (seen within one week) is required if there is **proliferative** retinopathy or there is evidence of clinically significant **macular oedema (hard exudates** at the fovea).

## Screening:

### T1 DM:

- Newly diagnosed DM → after 5 years
- From 5-10 years → annual
- More than 10 years → 6 monthly

### T2 DM:

- Annually

Nonproliferative diabetic retinopathy, with scattered intraretinal dot-blot and flame hemorrhages, along with macular exudates. Macular exudates can be related to diabetic macular edema, which accounts for a large portion of poor vision and disability secondary to diabetic retinopathy

# Pregnancy: diabetes mellitus

Diabetes mellitus may be a pre-existing problem or develop during pregnancy, gestational diabetes. It complicates **up to 1 in 20 pregnancies.**

NICE estimates the following breakdown:

- 87.5% have gestational diabetes
- 7.5% have type 1 diabetes
- 5% have type 2 diabetes

**Risk factors for gestational diabetes:**

- **BMI of > 30 kg/m$^2$**
- **Previous macrosomic baby weighing 4.5 kg or above.**
- **Previous gestational diabetes**
- **First-degree relative with diabetes**
- Ethnic origin (South Asian, black Caribbean and Middle Eastern)

**Screening for gestational diabetes:**

- The 2-hour 75 g oral glucose tolerance test **(OGTT) is used to diagnose gestational diabetes definitively.**
- If a woman has had gestational diabetes previously an oral glucose tolerance test **(OGTT)** should be performed at **16-18 weeks** and at **28 weeks if the first test is normal.**
- Women with any of the other risk factors should be offered an OGTT at 24-28 weeks.
- Currently the same WHO diagnostic criteria are used as for non-pregnant patients.
- There is however increasing evidence that a lower threshold should be used as treating borderline patients improves both maternal and neonatal outcomes.

**Diagnostic thresholds for gestational diabetes**

- fasting glucose is >= 5.6 mmol/L
- 2-hour glucose is >= 7.8 mmol/L
- **If fasting blood glucose between 5.5 and 7.0 mmol/l then proceed to >> 75-g oral glucose tolerance test**

**Management of gestational diabetes:**

- newly diagnosed women should be seen in a joint diabetes and antenatal clinic within a week
- women should be taught about self-monitoring of blood glucose
- advice about diet (including eating foods with a low glycaemic index) and exercise should be given
- **if the fasting plasma glucose level is < 7 mmol/l** a trial of diet and exercise should be offered

  - if glucose targets are not met within 1-2 weeks of altering diet/exercise metformin should be started
  - if glucose targets are still not met **insulin should be added** to diet/exercise/metformin
  - gestational diabetes is treated with short-acting, not long-acting, insulin
- if at the time of diagnosis the fasting glucose level is >= 7 mmol/l **insulin should be started**
- if the plasma glucose level is between 6-6.9 mmol/l, and there is evidence of complications such as macrosomia or hydramnios, insulin should be offered
- glibenclamide should only be offered for women who cannot tolerate metformin or those who fail to meet the glucose targets with metformin but decline insulin treatment

**Management of pre-existing diabetes:**

- Weight loss for women with BMI of > 27 kg/m^2
- **Stop oral hypoglycemic agents, apart from metformin** and possible sulphonylureas and **commence insulin.**
- **Folic acid 5 mg/day from pre-conception to 12 weeks gestation.**
- **Detailed anomaly scan** at **18-20 weeks** including **four-chamber view of the heart and outflow tracts.**
- Tight glycemic control reduces complication rates
- Treat retinopathy as can worsen during pregnancy

**Complications**

- Macrosomia (the commonest c omplications)
- defined by a birth weight > 4.5Kg
- affects up to 45% of babies
- **shoulder dystocia is a common delivery problem occurring in up to 15- 20% of cases.**
- Neonatal hypoglycaemia
- Maternal complications are hypertension, preeclampsia, increased risk of developing diabetes mellitus and increased risk of cesarean delivery.

Summary of Targets for self monitoring of pregnant women (pre-existing and gestational diabetes)

| Time | Target |
|---|---|
| Fasting | 5.3 mmol/l |
| 1 hour after meals | 7.8 mmol/l, or: |
| 2 hour after meals | 6.4 mmol/l |

**DM >>> firstly** manage with **low carbohydrate Diet and exercise, 2nd**: Metformin, Daonil or insulin (Regular & NPH).

# DVLA: diabetes mellitus

**Until recently** people with **diabetes** who used **insulin could not hold a HGV** licence

The DVLA **changed** the rules in **October 2011.** The following standards need to be met (and **also** apply to patients using other **OHG** such as sulfonylureas):

- There has **not been any episode of severe hypoglycaemic** event requiring the assistance of another person in **the previous12 months.**
- The driver has **full hypoglycaemic awareness**
- The driver must show **evidence of adequate glycaemic control** by regular blood glucose monitoring*, at least **twice daily** and at times relevant to driving.
- The driver must demonstrate an **understanding of the risks** of **hypoglycaemia** and **the ability to manage hypoglycaemia independently.**
- Here are no other debarring complications of diabetes.

From a practical point of view patients on insulin who want to apply for a Group 2 (HGV) (Heavy Goods Vehicles) licence need to complete a D2 form. They may will also be required to produce a D4 Medical examination report.

**Other specific points for group 1 drivers:**

- If on insulin then patient can drive a car as long as they have hypoglycaemic awareness, not more than one episode of hypoglycaemia requiring the assistance of another person within the preceding 12 months and no relevant visual impairment. Drivers are normally contacted by DVLA.
- If on tablets or **exenatide no** need to notify DVLA.
- If tablets may induce hypoglycaemia (e.g. sulfonylureas) then there must not have been more than one episode of hypoglycaemia requiring the assistance of another person within the preceding 12 months.
- If diet controlled alone then no requirement to inform DVLA.

*To demonstrate adequate control, the Secretary of State's Honorary Medical Advisory Panel on Diabetes Mellitus has recommended that applicants will need to have used **blood glucose meters** with **a memory function** to measure and record blood glucose levels **for at least 3 months** prior to submitting their application.

Patients on insulin >>> may **now** hold a HGV licence if they meet strict DVLA criteria relating to hypoglycemia i.e. **he can keep his HGV licence after discussion with the DVLA.**

# Hypoglycaemia

## Monomer: EXPLAIN

**EX (exogenous insulin) P (pituitary) L (liver diseases) A (addison, alcohol) IN (insulinoma).**

## Causes

- insulinoma - increased ratio of proinsulin to insulin
- self-administration of insulin/sulphonylureas
- liver failure
- Addison's disease
- alcohol
- nesidioblastosis - beta cell hyperplasia

## Physiological response to hypoglycaemia

- hormonal response: the first response of the body is decreased insulin secretion. This is followed by **increased glucagon secretion.** Growth hormone and cortisol are also released but later
- sympathoadrenal response: increased catecholamine-mediated (adrenergic) and acetylcholine-mediated (cholinergic) neurotransmission in the peripheral autonomic nervous system and in the central nervous system

## Features

- blood glucose levels and the severity of symptoms are not always correlated, especially in patients with diabetes.
- blood glucose concentrations <3.3 mmol/L cause autonomic symptoms due to the release of glucagon and adrenaline (average frequency in brackets):
    - Sweating
    - Shaking
    - Hunger
    - Anxiety
    - Nausea
- blood glucose concentrations below <2.8 mmol/L cause neuroglycopenic symptoms due to inadequate glucose supply to the brain:
    - Weakness
    - Vision changes
    - Confusion
    - Dizziness
- Severe and uncommon features of hypoglycaemia include:
    - Convulsion
    - Coma

## Management of hypoglycaemia

- **the following guidelines are based on the BNF hypoglycaemia treatment summary.**
- in the community (for example, diabetes mellitus patients who inject insulin):
  - **Initially, oral glucose 10-20g should be given in liquid, gel or tablet form**
  - Alternatively, a propriety quick-acting carbohydrate may be given: GlucoGel or Dextrogel.
  - A 'HypoKit' may be prescribed which contains a syringe and vial of glucagon for IM or SC injection at home
- **in a hospital setting:**
  - **If the patient is alert, a quick-acting carbohydrate may be given (as above)**
  - If the patient is unconscious or unable to swallow, subcutaneous or intramuscular injection glucagon may be given.
  - Alternatively, intravenous 20% glucose solution may be given through a large vein.

# Insulinoma

An insulinoma is a neuroendocrine tumour deriving mainly from pancreatic Islets of Langerhans cells (β cells).

## Basics:

- Most common pancreatic endocrine tumour (50%).
- 10% malignant, 10% multiple.
- More common in females.
- Of patients with multiple tumours, **50% have MEN-1.**
- Incidence 1-2/million/year.

## Features: (a one-year history of weight gain and intermittent sweating)

- Features of **hypoglycaemia (e.g., feel hungry, sweaty, tremors, diplopia,** weakness etc.): **typically, early in morning** or **just before meal.**
- **Rapid weight gain** may be seen (~ 5 kg over the past 6 months)
- **High insulin.**
- **High C-peptide.**
- **Raised Proinsulin: insulin ratio.**

## Diagnosis:

- **Supervised, prolonged fasting (up to 72 hours).**
- CT pancreas: 90% of Insulinoma are **less than 2 cm** in size.

## Management:

- Surgery.
- Diazoxide and **somatostatin** if patients are not candidates for surgery.

**EX. A typical presentation of Insulinoma**: A 47-year-old woman is referred to the general medical clinic. She has **gained 10 kg in weight in the past 3 months** but her main problem is **episodic sweating and hunger**. These episodes of sweating are associated with **double vision** and **typically occur early in the morning**. Clinical examination is **unremarkable** >>>? **Insulinoma** >>> She requires **confirmation** of the suspected diagnosis and this should be undertaken with a **72 hour fast.**

**If** the patient develops **symptoms** >>> then a **plasma glucose** is measured and **if low** >>> **Insulin** and **C-peptide** is then collected and the fast terminated.

**Measuring insulin and C-peptides with a normal glucose level** would provide **no meaningful** information. First we have to see whether she actually becomes hypoglycaemic.

**So if suspect Insulinoma >>> so firstly confirm by 72 hour fast.**

**NB:** Hyperinsulinaemia in the absence of raised C-peptide >>> highly suggestive of Insulin misuse.

**NB:** Elevation of both insulin and C-peptide may raise suspicion of sulphonylureas abuse >>> It is possible to assay urinary SU levels.

### Glucagon:

Glucagon is designed to **increase provision of energy in a time of need.**

Glucagon **stimulates lipolysis.**

Glucagon leads to **stimulation of catecholamine** secretion.

It **delays gastric emptying** and **reduces pancreatic exocrine secretions**.

With respect to **glucose handling**, glucagon stimulates glycogenolysis, at the same time inhibiting glycolysis and activating gluconeogenesis >> ↑**Glucose**.

Used in **severe hypoglycemia** >> 1 mg (1 U) IM/SC/IV, repeat every 20 min once or twice.

Used in **βB** or **CCB toxicity** >>> IVI loading and maintenance dose.

## Glucagonoma

- Patient with **DM** with the **characteristic rash of Necrolytic Migratory Erythema (NME)**, therefore this diabetes may be secondary to a Glucagonoma.
- Glucagonoma is **extremely rare 1/20 million.**
- Most primary tumours are **> 3 cm** in diameter, **70% are malignant** and more than **50% have metastasised** at the time of diagnosis.
- Diagnosis is confirmed by **raised plasma glucagon level.**
- Abdomen US or CT or Octreotide scanning for localization.
- **Treatment:**
  - The potential for surgical cure is only 5%.

- Octreotide is useful in controlling the rash.
- Palliative chemotherapy.
- TACE via hepatic artery

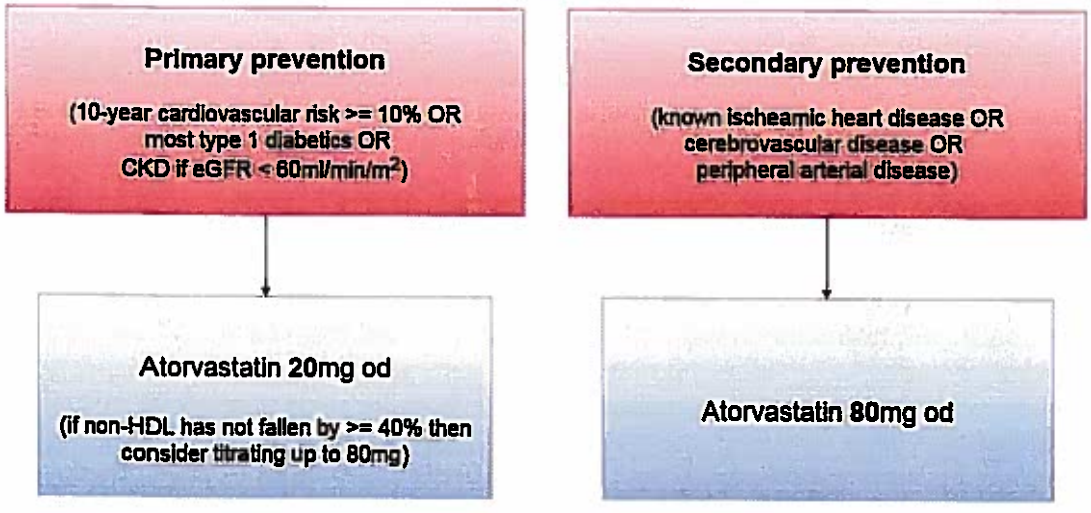
## Hyperlipidaemia: Management

**Normal values:**

- TC < 5 mmol/l
- TG < 2 mmol/l
- LDL-C < 3 mmol/l
- HDL-C > 1 mmol/l

**In the primary prevention of CVD using statin aim for a reduction in non-HDL cholesterol of>40%**

Graphic showing choice of statin.




## Primary prevention - who and how to assess risk.

**population groups:**

- people treated for HIV
- people with serious mental health problems
- people taking medicines that can cause dyslipidaemia such as antipsychotics, corticosteroids or immunosuppressant drugs
- people with autoimmune disorders/systemic inflammatory disorders such as systemic lupus erythematosus

## Special situations

### Type 1 diabetes mellitus

- NICE recommend that we 'consider statin treatment for the primary prevention of CVD in all adults with type 1 diabetes'
- atorvastatin 20 mg should be offered if type 1 diabetics who are:
  - older than 40 years, or
  - have had diabetes for more than 10 years or
  - have established nephropathy or
  - have other CVD risk factors

### Chronic kidney disease (CKD)

- atorvastatin 20mg should be offered to patients with CKD
- increase the dose if a greater than 40% reduction in non-HDL cholesterol is not achieved and the eGFR > 30 ml/min. If the eGFR is < 30 ml/min a renal specialist should be consulted before increasing the dose

### how and who to asses the risk score:

NICE recommend we use the **QRISK2** CVD risk assessment tool for patients aged <= 84 years. Patients >= 85 years are at high risk of CVD due to their age. **QRISK2** should not be used in the following situations as there are more specific guidelines for these patient groups:

- type 1 diabetics.
- patients with an estimated glomerular filtration rate (eGFR) less than 60 ml/min and/or albuminuria.
- patients with a history of familial hyperlipidemia.

## Interpreting the QRISK2 result

Probably the headline change in the 2014 guidelines was the new, lower cut-off of 10-year CVD risk cut-off of 10%.

**NICE now recommend we offer a statin to people with a QRISK2 10-year risk of >= 10%**

Lifestyle factors are of course important and NICE recommend that we give patients the option of having their CVD risk reassessed after a period of time before starting a statin.

**Atorvastatin 20mg should be offered first-line.**

**NICE suggest QRISK2 may underestimate CVD risk in the following population groups:**

- people treated for HIV
- people with serious mental health problems
- people taking medicines that can cause dyslipidaemia such as antipsychotics, corticosteroids or immunosuppressant drugs
- people with autoimmune disorders/systemic inflammatory disorders such as systemic lupus erythematosus

## Measuring lipid levels

When measuring lipids both the total cholesterol and HDL should be checked to provide the most accurate risk of CVD. A full lipid profile should also be checked (i.e., including triglycerides) before starting a statin. **The samples do not need to be fasting.**

In the vast majority of patients the cholesterol measurements will be fed into the **QRISK2 tool.** If, however, the patient's cholesterol is very high we should consider familial hyperlipidemia.

### NICE recommend the following that we should consider the possibility of familial hypercholesterolaemia and investigate further if:

- the total cholesterol level greater than 7.5 mmol/L and/or
- there is a personal or family history of premature coronary heart disease (an event before 60 years in an index person or first-degree relative [parents, siblings, children

## Follow-up of people started on statins

NICE recommend we follow-up patients at 3 months

- repeat a full lipid profile
- if the non-HDL cholesterol has not fallen by at least 40% concordance and lifestyle changes should be discussed with the patient
- NICE recommend we consider increasing the dose of atorvastatin up to 80mg

## Lifestyle modifications

These are in many ways predictable but NICE make a number of specific points:

### Cardioprotective diet

- total fat intake should be <= 30% of total energy intake
- saturated fats should be <= 7% of total energy intake
- intake of dietary cholesterol should be < 300 mg/day
- saturated fats should be replaced by monounsaturated and polyunsaturated fats where possible
- replace saturated and monounsaturated fat intake with olive oil, rapeseed oil or spreads based on these oils
- choose wholegrain varieties of starchy food
- reduce their intake of sugar and food products containing refined sugars including fructose
- eat at least 5 portions of fruit and vegetables per day
- eat at least 2 portions of fish per week, including a portion of oily fish
- eat at least 4 to 5 portions of unsalted nuts, seeds and legumes per week

### Physical activity

- each week aim for at least 150 minutes of moderate-intensity aerobic activity or 75 minutes of vigorous-intensity aerobic activity or a mix of moderate and vigorous aerobic activity
- do muscle-strengthening activities on 2 or more days a week that work all major muscle groups (legs, hips, back, abdomen, chest, shoulders and arms) in line with national guidance for the general population

### Weight management

- no specific advice is given, overweight patients should be managed in keeping with relevant NICE guidance

### Alcohol intake

- again no specific advice, other than the general recommendation: men and women are advised not to drink more than 14 units a week on a regular basis

### Smoking cessation

- smokers should be encouraged to quit

## Secondary prevention manaaement

- All patients with CVD should be taking a statin in the absence of any contraindication.
- Atorvastatin 80mg should be offered first-line.
- Follow-up patients at 3 months: if the non-HDL cholesterol has not fallen by at least 40% >> ↑ the dose of atorvastatin gradually up to 80mg.

### Targets of manaaement

| | Total cholesterol | LDL cholesterol | Triglycerides |
|---|---|---|---|
| Joint British Societies | < 4.0 mmol/1 | < 2.0 mmol/1 | < 1.7 mmol/L |

**EX: Markedly raised triglycerides + Xanthoma + recurrent** episodes of **upper abdominal pain**, nausea and vomiting + Family history of abdominal pain >>> **Chylomicronaemia syndrome >>>** it is due to a circulating **inhibitor** of lipoprotein lipase (type 1c hyperlipidaemia). It typically presents with eruptive xanthoma and abdominal colic. Complications include **retinal vein occlusion, acute pancreatitis**, and steatosis and lipidaemia retinalis.
**Treatment: Fibrates.**
**EX.** A **10-year risk of ≥ 20%** is used to identify patients who should be considered for lipid-lowering therapy. >> **Simvastatin 40mg OD** is the first line treatment in patients with a significant risk. With **no target level** for total cholesterol or LDL-cholesterol for **primary** prevention.

**EX:** Pt. had a myocardial infarction 6 months ago presents for review. He should has target cholesterol levels to be:

- **Total cholesterol of < 4 mmol/l.**
- **LDL cholesterol of < 2 mmol/l.**
- **TG < 1.7 mmol/l**

**EX:** Pt with **subclinical hypothyroidism** (↑TSH with normal fT4) plus **dyslipidaemia** >>> the most appropriate treatment for this dyslipidaemia is **Thyroxine.**
Thyroid hormone is known to play a role in regulating the synthesis, metabolism, and mobilisation of lipids. It is recognised that **the lipid abnormalities tend to resolve following treatment with thyroxine.**

**NB: HDL:**
**Women** has naturally higher HDL compared to men due to estrogen ☺
**COCP** also increase HDL ☺
**Exercise** is effective in raising HDL levels ☺
**Mild to moderate alcohol consumption** is associated with increase in HDL
**DM** (even **diet controlled DM**) causes lowered HDL and raised TG, but the TC level may be normal ☹

## Secondary hypertriglyceridaemia

### Causes of predominantly hypercholesterolemia:

- **Nephrotic syndrome.**
- **Hypothyroidism.**
- **Cholestasis.**

### Causes of predominantly hypertriglyceridaemia:

- **Obesity**
- **Alcohol**
- **Diabetes mellitus (types 1 and 2)**
- **Liver disease**
- **Chronic renal failure**
- Drugs: **thiazides,** non-selective beta-blockers, unopposed oestrogen

**Remnant hyperlipidaemia (type III hyperlipidaemia)**
**(Mixed hyperlipidaemia) (Dys-betalipoproteinaemia)**

### Overview:

- Also known as Fredrickson **type III hyperlipidaemia**, broad-beta disease and **dysbetalipoproteinaemia.**

- Rare cause of **Mixed** hyperlipidaemia (**raised cholesterol** typically 8-12 mmol/l **and triglyceride levels** typically 5-20 mmol/l).
- **Normal Apo B concentration.**
- Associated with **APO-E2 homozygosity** and occurs with a frequency of **1:100.**
- Definitive diagnosis is by **lipoprotein electrophoresis** or **genotyping of Apo-protein E.**
- It is transmitted as **autosomal recessive trait** and usually requires a secondary exacerbating metabolic factor for expression of the phenotype.
- Therefore **secondary causes of hyperlipidaemia** such as **obesity, DM, hypothyroidism**, renal insufficiency, high-calorie, high-fat diet or **alcohol** are often encountered at time of diagnosis.
- High incidence of **early onset** of age (around **30** yrs. old) for **ischaemic heart disease** and **peripheral vascular disease.**
- Thought to be caused by impaired removal of intermediate density lipoprotein (IDL) from the circulation by the liver.

## Features:

- **Palmer xanthomas** (yellow-orange discoloration of palm skin creases)
- **Tuberous xanthomas** (elbows and knees).

## Management:

- **Fibrates** are first line treatment.
- **Treatment** of the **secondary** causes.

**The commonest cause of a mild hypertriglyceridaemia is obesity secondary** to a reduced efficacy of lipoprotein lipase activity and overproduction of VLDL.

## Causes of predominantly hypertriglyceridaemia:

- **Obesity**
  - **The commonest cause of a mild hypertriglyceridaemia is obesity** secondary to a **reduced efficacy of lipoprotein lipase** activity and overproduction of VLDL.
  - **hypertriglyceridaemia and raised transaminases are suggestive of increased hepatic fat >> associated with Non-alcoholic steatohepatitis (NASH)**
- **type 2 diabetes mellitus**
  - **Bad diabetic control (↑↑ $HbA_{1c}$) >> ↓ activity of lipoprotein lipase (LPL) (because LPL requires insulin for full activity) >> hypertriglyceridaemia and low high-density lipoprotein (HDL)**
- Alcohol
- Chronic renal failure

- Drugs: thiazides, non-selective beta-blockers, unopposed oestrogen
- Liver disease

### Causes of predominantly hypercholesterolaemia

- Nephrotic syndrome
- Cholestasis
- **Hypothyroidism**
  - Frank hypothyroidism is said to occur in 4% of patients with dyslipidaemias;
  - **a raised thyroid-stimulating hormone (TSH)** & normal free T4 occur in 10% of patients with dyslipidaemia
  - Total cholesterol often improves to some degree with thyroxine therapy but statins might be required as well.

**High triglycerides and low high-density lipoprotein (HDL) cholesterol are the commonest lipid abnormality seen in type 2 diabetes,**

Hypercholesterolaemia rather than hypertriglyceridaemia: nephrotic syndrome, cholestasis, hypothyroidism

## Lipid-lowering agents

### Mechanism of action and adverse effects

The following table compares the side-effects of drugs used in hyperlipidaemia:

| Drugs | Mechanism of action | Adverse effects |
|---|---|---|
| Statins | HMG CoA reductase inhibitors | Myositis, deranged LFTs |
| Ezetimibe | Decreases cholesterol absorption in the small intestine | Headache |
| Nicotinic acid | Decreases hepatic VLDL secretion | Flushing, myositis |
| Fibrates | **Agonist of PPAR-alpha therefore increases lipoprotein lipase expression** | Myositis, pruritus, cholestasis |
| Cholestyramine | Decreases bile acid reabsorption in the small intestine, upregulating the amount of cholesterol that is converted to bile acid | GI side-effects |

**PPAR-α agonists (The fibrate)** >> ↓serum triglyceride levels and ↑ HDL-cholesterol
**PPAR-γ agonists** (the glitazones) >> ↓free fatty acid levels >> ↓insulin resistance >> ↓blood glucose levels

## Characteristic Xanthomata in hyperlipidaemia

### Palmar Xanthoma:

- **Remnant** hyperlipidaemia
- May less commonly be seen in familial hypercholesterolaemia.

### Eruptive Xanthoma:

- It is due to high **triglycerides** level and presents as multiple red/yellow vesicles on the **extensor surfaces** e.g. elbows and knees.
- Familial **hypertriglyceridemia.**
- **Lipoprotein lipase deficiency.**

### Tendon Xanthomas, tuberous xanthoma, xanthelasma:

- Familial hyper**cholesterol**aemia
- Remnant hyperlipidaemia

**The most clinical consistent sigh with isolated hypertriglyceridemia is Lipaemia retinalis** which is an association between **isolated hypertriglyceridemia** and a pale pink milky appearance to the retinal vessels or even to the retina itself.

Xanthelasma are also seen without lipid abnormalities.

### Managements of xanthelasma:

- Surgical excision
- Topical trichloroacetic acid
- Laser therapy
- Electrodesiccation

## Metabolic syndrome

Unfortunately there are a number of competing definitions of the metabolic syndrome around at the present time.

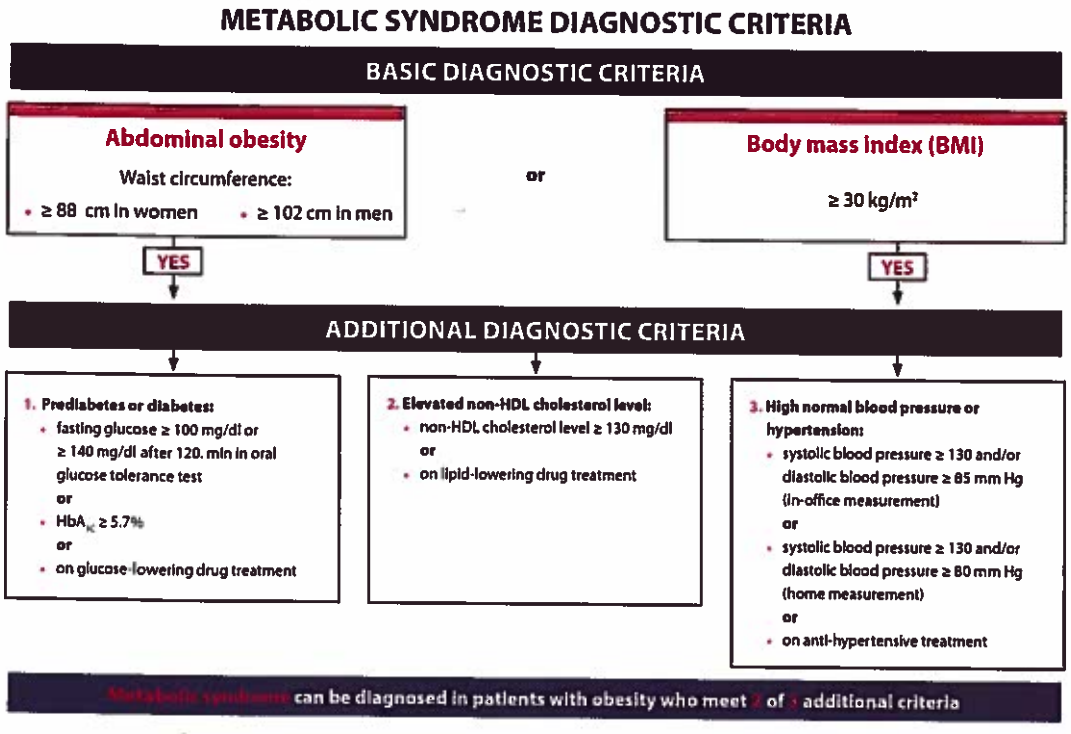
It is thought that the key pathophysiological factor is insulin resistance.

SIGN recommend using criteria similar to those from the American Heart Association. The similarity of the International Diabetes Federation criteria should be noted.

For a diagnosis of metabolic syndrome **at least 3 of the following** should be identified:

- **Elevated waist circumference: men > 102 cm, women > 88 cm.**
- **Elevated triglycerides: > 1.7 mmol/L.**

- **Reduced HDL**: < 1.03 mmol/L in males and < 1.29 mmol/L in females.
- **Raised blood pressure: > 130/85** mmHg, or active ttt of hypertension.
- **Raised fasting plasma glucose > 5.6** mmol/L (110 mg/dl), or previously diagnosed T2DM.


METABOLIC SYNDROME DIAGNOSTIC CRITERIA
BASIC DIAGNOSTIC CRITERIA
Abdominal obesity
Waist circumference:
• ≥ 88 cm in women
• ≥ 102 cm in men
YES
or
Body mass index (BMI)
≥ 30 kg/m²
YES
ADDITIONAL DIAGNOSTIC CRITERIA
1. Prediabetes or diabetes:
• fasting glucose ≥ 100 mg/dl or ≥ 140 mg/dl after 120. min in oral glucose tolerance test
or
• HbA1c ≥ 5.7%
or
• on glucose-lowering drug treatment
2. Elevated non-HDL cholesterol level:
• non-HDL cholesterol level ≥ 130 mg/dl
or
• on lipid-lowering drug treatment
3. High normal blood pressure or hypertension:
• systolic blood pressure ≥ 130 and/or diastolic blood pressure ≥ 85 mm Hg (in-office measurement)
or
• systolic blood pressure ≥ 130 and/or diastolic blood pressure ≥ 80 mm Hg (home measurement)
or
• on anti-hypertensive treatment
Metabolic syndrome can be diagnosed in patients with obesity who meet 2 of 3 additional criteria

- blood pressure: > 140/90 mmHg
- dyslipidaemia: **triglycerides:** > 1.695 mmol/L and/or high-density lipoprotein cholesterol (HDL-C) < 0.9 mmol/L (male), < 1.0 mmol/L (female)
- central obesity: waist:hip ratio > 0.90 (male), > 0.85 (female), and/or body mass index > 30 kg/m2
- microalbuminuria: urinary albumin excretion ratio > 20 mg/min or albumin:creatinine ratio > 30 mg/g

## Other associated features include:

- **Raised uric acid levels**
- **NASH:** Non-alcoholic fatty liver disease
- **PCOD:** Polycystic ovarian syndrome

**NB:** High LDL levels are not part of the International Diabetes Federation or the World Health Organization diagnostic criteria.

## Management

- Aggressive lifestyle modification focused on weight reduction and increased physical activity
- Long-term **exercise upregulates expression of GLUT4**, which may reduce hyperglycemia in patients with type 2 DM or metabolic syndrome.
- **Orlistat** (an inhibitor of gastrointestinal lipases) **with diet, reduces the risk of diabetes in an obese patients** by 38% more than diet alone.

**Alstrom syndrome (AS)**

- rare autosomal recessive disease
- caused by mutations in the ALMS1 gene.
- characterized by multiorgan dysfunction.

Key features are:

- **childhood obesity, hyperinsulinemia, early-onset type 2 diabetes, and hypertriglyceridemia.** Thus, AS shares several features with the common metabolic syndrome, namely obesity,
- blindness **due to congenital retinal dystrophy**,
- sensorineural hearing loss.
- dilated cardiomyopathy in over 60% of cases
- develo mental dela s in 50 % of cases.

# Obesity

## Appetite regulation (ghrelin and leptin)

**Leptin (the satiety hormone)**

- Produced by adipose tissue.
- Acts on ventromedial area of hypothalamus (satiety center) to ↓↓ appetite.
- Obese people have ↑↑ leptin due to ↑↑ adipose tissue but are tolerant or resistant to leptin's anorexigenic effect.
- Mutation of leptin gene >> severe obesity.
- Factors >> ↓↓ leptin
  - Starvation
  - Sleep deprivation

**Ghrelin (the hunger hormone)**

- **Produced by stomach**
- **Acts on hypothalamus** to ↑↑ **hunger,** ↑↑ gastric acid secretion and ↑↑ **GIT motility. Acts synergistically with GnRH to stimulate growth hormone release**
- Regulate appetite >> stimulates hunger
- Factors >> ↑↑ ghrelin
  - Empty stomach (fasting)
  - Sleep deprivation
  - Prader-Willi syndrome
- Factors >> ↓↓ ghrelin
  - Stretched stomach

**In obese person >>Obesity hormones & appetite:**

- **L**eptin **L**owers appetite
- **G**hrelin **G**ains appetite

## BMI:

| | | BMI (Kg/m2) |
|---|---|---|
| 1 | Normal | 18 – 25 |
| 2 | Overweight | 25 – 30 |
| 3 | Obesity I | 30 – 35 |
| 4 | Obesity II | 35 – 40 |
| 5 | Obesity III (Morbid Obesity) | > 40 |

The **average daily energy consumption** of a **male** is **2500** kcal and **2000** kcal for a **female.**

Endocrinal causes of weight gain: **Cushing's** syndrome, **PCO, Hypothyroidism** and **Hypothalamic** disease (brain trauma or neoplasia).

# Medical treatments of obesity

## Orlistat:

- Orlistat is a **pancreatic lipase inhibitor** used in the management of obesity.
- Adverse effects include faecal urgency/incontinence and flatulence.
- A lower dose version is now available without prescription ('Alli').
- **NICE** have defined criteria for the use of Orlistat. It should only be prescribed as part of an overall plan for managing obesity in adults who have:
  1) BMI of > **30** kg/m2 who has tried at least **3** months of diet and life style modifications, or
  2) BMI of > **28** kg/m2 **with** associated **risk factors (as DM, HTN, IHD, OSA)**, or
  3) Continued weight loss e.g. at least 5% at 3 months.
  4) Orlistat is normally used for < 1 year.

If patients fail to lose at least 5% of their bodyweight within 3 months, orlistat should be discontinued.

## Sibutramine:

- **Withdrawn** January 2010 by the European Medicines Agency due to an increased risk of **cardiovascular events.**
- **Centrally acting appetite suppressant** (inhibits uptake of serotonin and noradrenaline at hypothalamic sites that regular food intake).
- Adverse effects include **hypertension** (monitor BP and pulse during treatment), constipation, headache, dry mouth, insomnia and anorexia.
- Contraindicated in psychiatric illness, **hypertension**, IHD, stroke, arrhythmias.

## Rimonabant:

- A specific CB1 cannabinoid receptor antagonist, was **withdrawn** in October 2008 after the European Medicines Agency warned of serious **psychiatric** problems including **suicide**.

**NB:**
- Combination ttt with anti-obesity drugs is not recommended.
- It should never be used as the sole element of treatment.
- Anti-obesity drug treatment should also be **discontinued** if weight loss is less than 5% after the first 3 months.
- Anti-obesity drug treatment should be **discontinued** if the individual regains weight at any time whilst receiving drug treatment.
- Diet and exercise have been shown to be **ineffective** over the long term.
- More than 90% of people who attempt to lose weight gain it all back.

# Obesity: bariatric surgery

The use of bariatric surgery in the management of obesity has developed significantly over the past decade.

It is now recognised that for many obese patients who fail to lose weight with lifestyle and drug interventions the risks and expense of long-term obesity outweigh those of surgery.

## NICE guidelines on bariatric surgery for adults:

**Consider surgery for people with severe obesity if:**

- They have a BMI of **40** kg/m2 or more, or
- Between **35** kg/m2 and 40 kg/m2 and other significant disease (for example, type 2 DM, and HTN) that could be improved if they lost weight.
- All appropriate non-surgical measures have failed to achieve or maintain adequate clinically beneficial weight loss for **at least 6 months.**
- They are receiving or will receive intensive specialist management.
- They are generally fit for anaesthesia and surgery.
- They commit to the need for long-term follow-up.
- Consider **surgery** as a **first-line option** for adults with **a BMI of more than 50 kg/m2** in whom surgical intervention is considered appropriate.
- Consider Orlistat **before** surgery if the waiting time is long.

**Obesity >>> NICE bariatric referral cut-offs:**

- With risk factors (T2DM, HTN etc.): **> 35** kg/m2.
- No risk factors: **> 40** kg/m2.

## Types of bariatric surgery:

- **Primarily restrictive**: **laparoscopic-adjustable gastric banding (LAGB)** or **sleeve gastrectomy (SG).**
- **Primarily malabsorptive**: classic biliopancreatic diversion (BPD) has now largely been replaced by **bilio-pancreatic diversion with duodenal switch.**
- **Mixed: Roux-en-Y gastric bypass surgery.**

## Which operation?

- **LAGB** produces **less** weight loss than malabsorptive or mixed procedures but as it has **fewer** complications it is normally **the first-line intervention** in patients with a **BMI of 30-39kg/m2.**

- Patients with a BMI > 40 kg/m2 may be considered for a gastric bypass or sleeve gastrectomy. The latter may be done as a sole procedure or as an initial procedure prior to bypass.
- Primarily malabsorptive procedures are usually reserved for very obese patients (e.g. BMI > 60 kg/m2)

Bilio-pancreatic diversion with duodenal switch >>> is a primarily malabsorptive procedure which reserved only for patients who are very obese (BMI > 60 kg/m2).

The **duodenum** is the primary site of absorption for both **iron** and **calcium.**
**All gastric bypass operations bypass the duodenum.**
Nearly all menstruating women will therefore require **iron supplementation.**

# Acute phase proteins

## Acute phase proteins

- CRP*
- procalcitonin
- ferritin
- fibrinogen
- alpha-1 antitrypsin
- caeruloplasmin
- serum amyloid A
- haptoglobin
- complement

During the acute phase response the liver decreases the production of other proteins (sometimes referred to as negative acute phase proteins). Examples include:

- albumin
- transthyretin (formerly known as prealbumin)
- transferrin
- retinol binding protein
- cortisol binding protein

*Levels of CRP are commonly measured in acutely unwell patients. CRP is a protein synthesized in the liver and binds to phosphocholine in bacterial cells and on those cells undergoing apoptosis. In binding to these cells, it is then able to activate the complement system. CRP levels are known to rise in patients following surgery. However, levels of greater than 150 at 48 hours post operatively are suggestive of evolving complications.

## Galactosaemia

Galactosaemia is a rare autosomal recessive condition caused by the absence of galactose-1-phosphate uridyl transferase. This results in intracellular accumulation of galactose-1-phosphate

### Features

- jaundice
- failure to thrive
- hepatomegaly
- cataracts
- hypoglycaemia after exposure to galactose
- Fanconi syndrome

**Diagnosis:** urine reducing substances

**Management** is with a galactose free diet

## Familial hypertriglyceridaemia

### Overview

- autosomal dominant condition
- Affects 1 in 300 people.
- Usually due to polygenic factors
- May also be due to **lipoprotein lipase deficiency**
- can be exacerbated by:
  - alcohol,
  - glucocorticoids and
  - thiazide diuretics

### Pathogenesis

- Hepatic over production of VLDL
- ↓ lipoprotein lipase (a potent metabolizer of triglycerides within VLDL) >> accumulation of VLDL molecules and triglycerides.

### Features

- Premature atherosclerosis
- Acute pancreatitis if triglyceride levels is very high (>11 mmol/l), likely due to pancreatic capillary obstruction.
- Features of hyperglycemia (due to abnormal glucose tolerance and insulin resistance)
- Eruptive xanthornas (yellow papules usually seen on the back, chest, and proximal extremities).

- **Lipaernia retinalis** (pale pink milky appearance to the retinal vessels or even to the retina itself).
- Retinal vein thrombosis

### Diagnosis

#### Lipid profile

- **raised very-low-density lipoprotein (VLDL) and triglyceride levels.**
- total cholesterol and LDL levels are typically normal

### Management

- first-line >> fibrates
- statins if there is mixed hyperlipidaemia

## Familial hypercholesterolaemia

Familial hypercholesterolaemia (FH) is an **autosomal dominant** condition that is thought to affect **around 1 in 500 people**.
It results in high levels of LDL-cholesterol which, if untreated, may cause early cardiovascular disease (CVD).
FH is caused by mutations in the gene which encodes the LDL-receptor protein.

### Case finding:

- NICE suggest that we should suspect FH as a possible diagnosis in adults with:
  - a total cholesterol level greater than 7.5 mmol/l and/or
  - a personal or family history of premature coronary heart disease (an event before 60 years in an index individual or first-degree relative)
- children of affected parents:
  - if one parent is affected by familial hypercholesterolaemia, arrange testing in children by age 10
  - if both parents are affected by familial hypercholesterolaemia, arrange testing in children by age 5

**Clinical diagnosis** is now based on the **Simon Broome criteria**:

- in adults total cholesterol (TC) > 7.5 mmol/l and LDL-C > 4.9 mmol/l or children TC > 6.7 mmol/l and LDL-C > 4.0 mmol/l, plus:
- for definite FH: tendon xanthoma in patients or 1st or 2nd degree relatives or DNA-based evidence of FH
- for possible FH: family history of myocardial infarction below age 50 years in 2nd degree relative, below age 60 in 1st degree relative, or a family history of raised cholesterol levels

## Management

- the use of CVD risk estimation using standard tables is not appropriate in FH as they do not accurately reflect the risk of CVD
- referral to a specialist lipid clinic is usually required
- high-dose statins are usually used first-line
- first-degree relatives have a 50% chance of having the disorder and should therefore be offered screening. This includes children who should be screened by the age of 10 years if there is one affected parent
- statins should be discontinued in women 3 months before conception due to the risk of congenital defects

Lipid-lowering therapy in patients with ACS: *(2019 ESCIEAS Guidelines for the management of dys/ipidaemias)*

- For patients who present with an **ACS,** and whose **LDL-C levels** are not at goal despite already taking a **maximally tolerated statin dose and ezetimibe,** adding a **PCSK9 inhibitor** early after the event (if possible, during hospitalization for the ACS event) should be considered.

# Hyperuricaemia

Increased levels of uric acid may be seen secondary to either increased cell turnover or reduced renal excretion of uric acid. Hyperuricaemia may be found in asymptomatic patients who have not experienced attacks of gout

Hyperuricaemia may be associated with hyperlipidaemia and hypertension. It may also be seen in conjunction with the metabolic syndrome

## Increased synthesis

- Lesch-Nyhan disease
- myeloproliferative disorders
- diet rich in purines
- exercise
- psoriasis
- cytotoxics

## Decreased excretion

- drugs: low-dose aspirin, diuretics, pyrazinamide
- pre-eclampsia
- alcohol
- renal failure
- lead

- **Lipaernia retinalis** (pale pink milky appearance to the retinal vessels or even to the retina itself).
- Retinal vein thrombosis

## Diagnosis

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## Management

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- pre-eclampsia
- alcohol
- renal failure
- lead

# ELECTROLYTES CHECKLIST

## Hypercalcaemia: causes

### The most common causes of hypercalcaemia are:

- **Malignancy** (bone metastases, myeloma, **PTHrP** from squamous cell lung cancer) and
- **Primary hyperparathyroidism** (**NOT** secondary or tertiary type).

### Other causes include

- Granulomas: **Sarcoidosis**, also Tuberculosis and histoplasmosis.
- **Vitamin D intoxication**
- Acromegaly
- **Thyrotoxicosis**
- **Milk-alkali syndrome**: Rennie antacid tablets and calcium tablets
- Drugs: **thiazides**, calcium containing antacids
- Dehydration
- **Addison's** disease
- **Paget's** disease of the bone: usually Ca is normal, but hypercalcemia may occur with prolonged immobilization.

In **solid tumours** like breast cancer, **hypercalcaemia** is caused by **tumour production** of **PTHrP** (parathyroid hormone-related protein). This acts on **osteoclasts** in bones to increase bone resorption and promote ca release from bone. It also inhibits ca excretion in the distal tubule of the kidney.
Hypercalcaemia of malignancy is **NOT** thought to be a product widespread bony metastasis and bone destruction, or tumour production of PTH or Vit D.

PTH-related peptide can be raised in a number of malignancies. Old PTH assays may have also picked up PTH-rp but **modern** assays are able to **distinguish** between the two.

The plasma **PTH** is the best single test for differentiating between hypercalcaemia due to **parathyroid** over activity and that due to **non-parathyroid** cause.

**Primary hyperparathyroidism** can be associated with a plasma PTH **within** the normal range.

The normal response to hypercalcemia due to **non-parathyroid cause** is **suppression** of the plasma PTH below the lower reference limit.

PTH levels within the reference limit or inappropriately high is suggestive of parathyroid disease.

PTH stimulates bone resorption and formation, whereas PTH-rp stimulates only bone resorption, with very low osteoblastic activity, and thus **ALP levels are usually within the normal range.**

So in malignancy: ↑ **Ca** with **low PTH** and **normal ALP**.

**EX:** Male patient 50 years old, well and fit, just takes OTC multivitamins, has **high serum ca** and **PTH is within normal >>> Primary hyperparathyroidism** (**NOT** Vit D excess).

So any Pt with high serum calcium >>> 1st check **PTH**, if **high or normal** so it is primary hyperparathyroidism, but if **suppressed** PTH so it is hypercalcaemia due to non-parathyroid cause.

If primary hyperparathyroidism >>> **Then** you should do **24 hours urinary calcium** or urinary calcium/creatinine ratio to distinguish primary hyperparathyroidism from FHH (see below).

FHH is often misdiagnosed as primary hyperparathyroidism but may be distinguished from the latter by the **positive family history** together with the **markedly low urine calcium excretion**.

**24 hours urinary calcium** or **urinary calcium/creatinine ratio** may be useful if used in comparison to the serum calcium in order to **distinguish** familial hypocalciuric hypercalcaemia (**FHH**) from primary hyperparathyroidism (it is **lower** than in 1ry hyperparathyroidism and the urinary calcium/creatinine ratio is usually **less** than 0.01).

It should be done as **first test** in **any patient with hypercalcaemia**.

FHH is a **benign** cause of hypercalcaemia and is a hereditary disease with **autosomal dominant** transmission with high penetrance, and is characterized by moderate chronic hypercalcaemia and normal or moderately elevated PTH.

The importance of this FHH condition is that the hypercalcaemia rarely leads to significant clinical signs and parathyroidectomy is unsuccessful as a therapy.

FHH is unlike hyperparathyroidism it is not associated with any specific abnormality, is benign and requires **no treatment**.

One of the key differentiating features between **myeloma** and monoclonal gammopathy of uncertain significance **(MGUS)** is the **absence of complications such as immune paresis, hypercalcaemia and bone pain.** **(So in MGUS >>> No hypercalcaemia)**

The **calcium-sensing receptor (CaSR)** is a G protein-coupled receptor, which allows the **parathyroid chief cell,** the **thyroidal C cells**, and the **ascending limb of loop of Henle** to respond to changes in the extracellular Ca concentration.
**Three** uncommon human disorders are due to abnormalities of the CaSR gene:
(1) FHH (Familial benign Hypocalciuric Hypercalcaemia).
(2) Neonatal severe hyperparathyroidism.
(3) Autosomal dominant hypocalcaemia with hypercalciuria.

**Primary** hyperparathyroidism is associated with hypercalcaemia and an inappropriately raised parathyroid hormone, the phosphate level is typically low.
**Secondary** hyperparathyroidism is associated with hypocalcaemia and an appropriately elevated parathyroid hormone level, the phosphate level is variable depending upon the aetiology (high in renal failure, low in vitamin D deficiency).

**Tertiary** hyperparathyroidism. Biochemically this is characterised by raised calcium, raised (or sometimes normal) phosphate and grossly elevated parathyroid hormone levels.

**Hypercalcaemia of malignancy and iatrogenic hypercalcaemia** would both be associated with a high calcium and low parathyroid hormone level.

## NB: Calculation of corrected calcium:

Add 0.1 mmol/L of calcium for every 4 g/dL that the albumin level is below 40 g/dL.

**EX**: Calcium = 2.6 mmol/L and serum albumin = 24 gm/L

| | |
|---|---|
| **Corrected calcium** | = 2.6 + (((40-24)/4) × 0.1) |
| | = 2.6 + ((16/4) × 0.1) |
| | = 2.6 + (4 × 0.1) |
| | = 2.6 + 0.4 |
| | **= 3.0 mmol/L** |

## Hypercalcaemia: management

- The initial management of hypercalcaemia is rehydration with **normal saline**, typically **3-4 litres/day**.
- Following rehydration **bisphosphonates** may be used like IV Zoledronic acid (Zometa 4 mg IVI). They typically take 2-3 days to work with maximal effect being seen at 7 days.
- Other options include: **calcitonin** - quicker effect than bisphosphonates, its use is limited by its association with **anaphylaxis,** and production of autoantibodies which reduce its effect by time. so **only** used in **resistant** cases.
- **Steroids** in sarcoidosis.
- **Furosemide** should only be given **with** fluid resuscitation. It is **calciuric.** It may be useful in patients who cannot tolerate aggressive fluid rehydration as in ventricular strain and pulmonary oedema.
- **Haemodialysis with low calcium bath.**
- **General measures**
  a. Minimize immobilization.
  b. Stop thiazide, NSAIDS and drugs that contains Ca & Vit D.

**Hypercalcaemia of malignancy:**
This is an **oncological emergency** affecting **20-40%** of patients with advanced cancer.
It is the most common life-threatening metabolic complication of malignancy.
Serum Ca++ **above 3 mmol/l** is associated with cardiac arrhythmia, coma, pancreatitis and urgent ttt is required.
**Hyporeflexia** is a common clinical sign in patients with significant hypercalcaemia (especially **more than 3 mmol**/L) (N= 2.2-2.6).
Other signs include the classic mnemonic **'bones, stones,** abdominal **groans** and psychic **moans'.**
**Abdominal pain** is commonly seen and there is increased risk of **acute pancreatitis.**
Also there is **nausea, vomiting, dehydration** and **polyuria, polydipsia (Nephrogenic DI)**

**NB:** Hypercalcaemia may induce **nephrogenic DI.**
**ECG: bradycardia, short QT interval,** prolonged PR interval (is possible, but is much less common than QT shortening.), widened T waves and arrhythmias **Ventricular fibrillation** has been reported in extreme cases.

**Bisphosphonates** inhibit bone resorption by **osteoclasts**, and are the **first** line pharmacological treatment of hypercalcaemia of malignancy. However, they **take 3-4 days** to reduce the calcium level, and **can result in worsening renal** function. It is therefore critical to **fully hydrate the patient prior to giving them** so in clinical practice we tend to give **3 litres of fluids over a 12-16 hrs period prior** to giving bisphosphonate. Clearly, this needs to be altered if the patient is at risk of fluid overload and cardiac failure.
Since Hypoalbuminaemia is common in malignancy and will affect the total serum Ca concentration, so use this **formula**:
**The corrected serum Ca =**
**Measured Ca (mmol/L) + (40-serum albumin gm/dl) X 0.027.**

**Hypercalcaemia** associated with **raised ALP** is more likely to be due to **bony metastases**;
**Hypercalcaemia** with **normal ALP** raises the possibility of **underlying** organ tumour like **myeloma**.

## Hyperparathyroidism

### Classification

| Type | PTH | Serum Ca | Serum Phos | Causes |
|---|---|---|---|---|
| Primary | Normal | High | Low | parathyroid adenoma |
| Secondary | High | Normal or Low | High | CRF >> vit D >> ↓ gut $Ca^{2+}$ absorption >> ↓ ca2+ >> ↑ PTH<br>CRF >> ↓ phosphate excretion >> hyperphosphatemia.<br>**Causes of ↓ Ca2+:**<br>• renal failure (most common)<br>• insufficient vit D,<br>• insufficient Ca2+ in the diet,<br>• excessive Mg2+ in the diet |
| Tertiary | High | High | High | **hyperplasia of the glands, and loss of response to ca2+.**<br>occurs after years of secondary hyperparathyroidism<br>**PTH is raised, calcium is raised and so is phosphate, whilst eGFR is significantly deceased** |

## 1- Primary hyperparathyroidism

In exams primary hyperparathyroidism is stereotypically seen in elderly females with an unquenchable **thirst** and **an inappropriately normal or raised parathyroid hormone level.** It is most commonly due to a solitary adenoma.

The prevalence of hyperparathyroidism is said to be **four per 1000 in women over 60**, and is 2 to 3 times more common in women than men.

| |
|---|
| The **PTH** level in **primary** hyperparathyroidism may be **normal** or less than twice the upper limit of normal. |
| A **high** or **even normal PTH** concentration **in the presence of hypercalcaemia** would support the diagnosis of primary hyperparathyroidism. |
| **Hypercalcaemia + elevated PTH + low phosphate** >>> indicating **primary hyperparathyroidism.**<br>The hypophosphatemia is due to the **reduced renal reabsorption of phosphate.** |
| When patient has grossly elevated calcium and in the context of the **extremely high PTH** concentration >>> **Parathyroid carcinoma** should be considered. |

**Causes of primary hyperparathyroidism:**

- 80%: **solitary adenoma**
- 15%: hyperplasia
- 4%: multiple adenoma
- 1%: carcinoma **(PTH is grossly elevated)**

**Features - 'bones, stones,** abdominal **groans** and psychic **moans':**

- **Polydipsia, polyuria**
- Peptic ulceration/**constipation/pancreatitis**
- **Bone pain/fracture**, especially if the PTH is elevated
- **Renal stones** and **renal medullary calcification.**
- **Depression, confusion**
- **Hypertension**

**Associations:**

- **Hypertension.**
- Multiple endocrine neoplasia: **MEN I and IIa.**

**Investigations:**

- raised calcium, low phosphate

- PTH may be raised or normal (inappropriately, given the raised calcium)
- technetium-MIBI subtraction scan
- pepperpot skull is a characteristic X-ray finding of hyperparathyroidism

**The effect of PTH on calcium and phosphate**

| Mechanism | calcium | Phosphate |
|---|---|---|
| **Excretion by kidneys** | Low | High |
| **Absorption from gut** | High | High |
| **Absorption from bone** | High | High |
| **Net Serum concentration** | **High** | **Low** |

**The PTH level in primary hyperparathyroidism may be normal**

**Phosphate is usually elevated or normal in bone metastases (this clue could differentiate primary hyperparathyroidism from cancer metastases**

### Treatment:

- **Total parathyroidectomy**.
- Bisphosphonates.

### Indications for parathyroidectomy including:

- **Serum** albumin-adjusted **calcium** greater than 0.25 mmol/L above the normal range (**Ionized Ca++ > 3 mmol/l**).
- **24 hour total urinary calcium excretion** greater than 10 mmol (400mg)
- **Creatinine clearance** reduced by 30% or more
- **DEXA Bone mineral density T-score less than −2.5 at any site**
- **Age less than 50**
- Unwillingness of patient to follow advice of medical surveillance.

**If unfit** for **surgery** >>> medical parathyroidectomy by **Cinacalcet** (which is used in **primary, secondary** and **tertiary** hyperparathyroidism).

Prior to any surgical intervention for hyperparathyroidism, it is crucial to **rule out phaeochromocytoma** as a co-existing diagnosis as in MEN 1 or 2a.

## 2- Secondary hyperparathyroidism

**Secondary hyperparathyroidism as in CKD** is with raised creatinine, borderline low calcium, and raised phosphate.

In secondary hyperparathyroidism, hypocalcaemia stimulates the parathyroid to produce excess PTH. **It may progress to tertiary hyperparathyroidism**, whereby the parathyroid becomes **autonomous** in producing PTH even without the stimulus of hypocalcaemia, but primary does not.

Phosphate retention and a lack of hydroxylated vitamin D drives increased levels of PTH as the body strives to retain calcium.

Patients with renal disease however are not treated for hyperparathyroidism **until the PTH level breaches twice the upper limit of the normal range**. This is because of the **risk** of **precipitating adynamic bone disease**.

A slightly elevated PTH level is actually desirable in the management of renal bone disease. **Suppression** is not generally necessary **until levels exceed 300 ng/L.**

Usual **first** line therapy is **weekly 1-Alphacalcidol,** because the drive for increased PTH comes at least in part from low levels of 1, 25-OH Vitamin D, and it is used when serum calcium is low-normal and PTH is above twice the upper limit of normal range.

If Vit D replacement fails to achieve a reduction of PTH levels, then **surgery** may be considered.

**Cinacalcet** is a PTH antagonist, it is a **calcimimetic** which is used to treat secondary hyperparathyroidism; It mimics the effect of calcium on the parathyroid glands (and elsewhere) with the intention of **limiting parathyroid hormone (PTH) production** and deleterious effects on bone architecture.

It is **only** recommended by NICE for the management of patients with hyperparathyroidism who are on dialysis and **not fit for surgery.**

## 3- Tertiary hyperparathyroidism

**In tertiary hyperparathyroidism:** ESRD with regular dialysis, when PTH production becomes autonomous, has marked **high PTH** (> twice upper normal), **high Calcium, high phosphate** >>> **TTT**: PTH antagonist **Cinacalcet,** in conjugation with other measures like a **low phosphate diet, phosphate binder such as Sevelamir**, but **only if** the patient is unable to undergo **surgery**.

I.e. The most appropriate treatment once **tertiary hyperparathyroidism** has developed is **parathyroidectomy**.

**EX**: ESRD Pt with ↑PTH and ↑ Ca >>> **TTT**: **Parathyroidectomy or Cinacalcet (only if not well fit for surgery).**

**Familial isolated hyperparathyroidism (FIHP):**
FIHP is a **rare** condition characterised by an **autosomal dominant** mode of inheritance. It is closely related to **MEN1** but the development of other tumours is not seen over the course of many years, despite the fact that a number of MEN1 germline mutations are now described.

**Parathyroidectomy** is the treatment of choice.

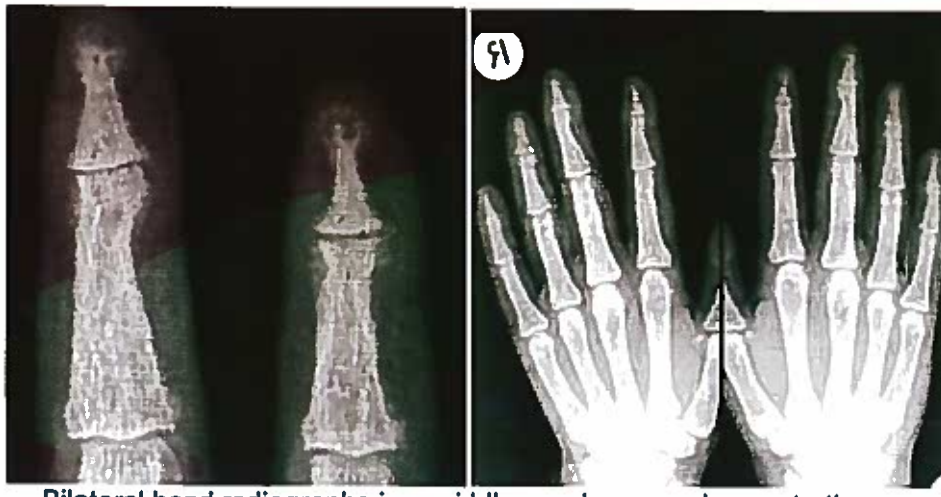
**EX**: A 45-year-old man is referred to the endocrine clinic. He has been found on **routine** screening to have an **isolated elevated calcium** of 2.9 mmol/L. There is no past medical history of note, and clinical examination is entirely normal. His father and uncle have been reported to have high calcium levels but had no other significant problems >>> **FIHP.**

**Hyperparathyroidism jaw tumour syndrome:**
It is a syndrome of hyperparathyroidism and fibro-osseous tumours of the jaw. It is described as having increased incidence in Romany families.

**Sevalamer** is a **non-aluminium containing phosphate binder**, and as such is a reasonable option for patients with ESRD with raised serum phosphate levels.

Aluminium hydroxide was previously the drug of choice, but due to concern about accumulation of aluminium, leading to possible aluminium related dementia, it has now fallen out of favour.

Alternatives to sevelamer include calcium acetate and calcium carbonate, although there are theoretical concerns about use of calcium containing salts and increased risk of tissue calcification



Bilateral hand radiographs in a middle-aged woman demonstrating generalised osteopenia, erosion of the terminal phalangeal tufts (acro-osteolysis) and subperiosteal resorption of bone particularly the radial aspects of the 2nd and 3rd middle phalanges. These changes are consistent with a diagnosis of hyperparathyroidism.

## Hypoparathyroidism

### Three types of hypothyroidism:

1. Primary Hypoparathyroidism.
2. Pseudo-hypoparathyroidism.
3. Pseudo-pseudo-hypoparathyroidism.

### 1- Primary Hypoparathyroidism:

- ↓ **PTH** secretion.
- E.g. secondary to thyroid surgery (N.B: this may seem an oxymoron, but most medical textbooks classify hypoparathyroidism which is secondary to surgery as being 'primary hypoparathyroidism').
- **Low calcium, high phosphate.**
- Treated with alfacalcidol.

**The main symptoms** of Hypoparathyroidism are **secondary to hypocalcaemia:**

- As extracellular calcium concentrations are important for muscle and nerve function many of the features seen in hypocalcaemia seen a result of **neuromuscular excitability**.
- Tetany: muscle twitching, cramping and **carpopedal spasm**
- **Paraesthesia** (usually **perioral** around mouth, fingers and toes)
- ECG: **prolonged QT interval**

- **With worsening hypocalcaemia:** Bronchospasm, Laryngospasm and Seizures.
- If **chronic >> depression, cataracts**
- **Trousseau's sign**: carpal spasm if the brachial artery occluded by inflating the blood pressure cuff and maintaining pressure above systolic. It is seen in around 95% of patients with hypocalcaemia and around 1% of normocalcaemic people
- **Chvostek's sign:** tapping over parotid causes facial muscles to twitch. It is seen in around 70% of patients with hypocalcaemia and around 10% of normocalcaemic people.

Hypocalcaemia >> **Trousseau's** sign is **more sensitive** and **specific** than Chvostek's sign

## 2- Pseudo-hypoparathyroidism:

- **Target cells** being insensitive to PTH **(insensitivity to PTH).**
- **Two types:**
  - **Type I:** there is a complete receptor defect.
  - **Type II:** the cell receptor is intact.
- **Due to abnormality in a Gs protein receptor (alpha unit).**
- **Autosomal dominant** fashion (It was previously thought to be an X-linked dominant condition).
- There is resistance to a variety of hormones that act via **cAMP** (including PTH, TSH and gonadotrophins).
- **Low calcium, high phosphate, high PTH (= same lab like 2ry hyperparathyroidism).**
- **Also** there is raised TSH with low T4 and raised gonadotrophins.
- Associated with (features): **low IQ, cognitive impairment, short stature, obesity, shortened 4th and 5th metacarpals,** brachymetacarpals, brachymetatarsals, **SC calcification nodules**, soft tissue calcification/ossification, **round face**, stocky habitus, and dental hypoplasia.
- Hypocalcaemia causes paraesthesia, cramps, tetany, and carpopedal spasm, whereas hypothyroidism causes fatigue.
- Diagnosis is made by **measuring urinary cAMP and phosphate levels following an infusion of PTH:**
  - In hypoparathyroidism this will cause an increase in both cAMP and phosphate levels.
  - In pseudohypoparathyroidism type I neither cAMP nor are phosphate levels increased.
  - Whilst in pseudohypoparathyroidism type II only cAMP rises but phosphate levels do not change.
- The mainstay of treatment is **calcium** and **vitamin D.**

The diagnosis is pseudo-hypoparathyroidism confirmed with **genetic analysis** and with a **failure of cAMP rise following PTH**.

### 3- Pseudo-pseudo-hypoparathyroidism:

- **Similar phenotype** to pseudohypoparathyroidism but **normal biochemistry**

## Hungry bone syndrome

Hungry bone syndrome is an uncommon entity but can occur after parathyroidectomy if the hyperparathyroidism has been long-standing.
The mechanism is thought to be thus: high pre-operative levels of parathyroid hormone provide a constant stimulus for osteoclast activity creating the hypercalcaemic state by de-mineralizing the bones.
This process can result in x-ray changes very similar to metastatic lytic lesions if left untreated. Upon removal of the parathyroid adenoma the **hormone levels fall rapidly** (they have a very short half-life) and the osteoclast activity is subsequently diminished and the bones rapidly begin re-mineralisation - 'hungry bone syndrome'.
This process can be uncomfortable and also result in systemic hypocalcaemia.

## Hypocalcaemia: causes and management

The clinical history combined with **PTH** levels will reveal the cause of hypocalcaemia in the majority of cases.

### Causes:

- **Vitamin D deficiency** (osteomalacia = ↓ s Ca + ↓ s phosphate + ↑ ALP) >> **Proximal myopathy** is often a presenting feature of osteomalacia.
- **Chronic renal failure**
- **Hypoparathyroidism** (e.g. post thyroid/parathyroid surgery)
- Pseudohypoparathyroidism (target cells insensitive to PTH)
- **Rhabdomyolysis (initial** stages)
- **Magnesium deficiency** (due to end organ PTH resistance), EX: Cisplatin.
- Massive blood transfusion.
- Acute pancreatitis may also cause hypocalcaemia.
- Contamination of blood samples with EDTA may also give falsely low calcium levels.

## Features

- tetany: muscle twitching, cramping and spasm
- perioral paraesthesia
- if chronic: depression, cataracts
- **ECG: prolonged QT interval**

## Trousseau's sign

- carpal spasm if the brachial artery occluded by inflating the blood pressure cuff and maintaining pressure above systolic
- wrist flexion and fingers are drawn together
- **seen in around 95% of patients with hypocalcaemia and around 1% of normocalcaemic people**

## Chvostek's sign

- tapping over parotid causes facial muscles to twitch
- seen in around 70% of patients with hypocalcaemia and around 10% of normocalcaemic people

| Findings | Conditions |
|---|---|
| Low PTH, ↑ Phosphate | Hvoooarathvroidism (e.q., oostsurqical) |
| High PTH, ↑ Phosphate | Hyperphosphatemia Pseudohypoparathyroidism |
| Hiqh PTH, ↑ Phosphate, ↑ Creatinine | Chronic kidney disease |
| Hiqh PTH, ↓ Maqnesium | Malabsorption or alcoholism |

## Management:

- Acute management of severe hypocalcaemia is with IV replacement. The preferred method is with **IV calcium gluconate, 10ml of 10% solution over 10 minutes.**
- IV calcium chloride is more likely to cause local irritation.
- ECG monitoring is recommended.
- Further management depends on the underlying cause.

# Hypomagnesaemia

Most of the body's magnesium is **intracellular** with **only 1% being extracellular**, in blood and interstitial fluid.
This means that blood magnesium levels do not necessarily correspond with whole body magnesium status.

## Cause of low magnesium:

- **Drugs: diuretics, cisplatin, cyclosporine** and cardiac glycosides
- **Malabsorption syndromes**

- **Diarrhoea**
- **Hypokalaemia, hypocalcaemia**
- **Total parenteral nutrition**
- **Alcohol**
- **Metabolic acidosis**
- **Renal diseases:** pyelonephritis, GN, ATN and interstitial nephritis.

**Features:**

- Paraesthesia
- Tetany
- Seizures
- Arrhythmias
- Lethargy, fatigue, muscle weakness, fasciculations
- changes in personality
- Lack of appetite.
- Decreased PTH secretion → **hypocalcaemia**
- ECG features similar to those of hypokalaemia
- Exacerbates digoxin toxicity

## Vitamin D resistant rickets

Vitamin D-resistant rickets is an **X-linked dominant** condition which usually presents in **infancy** with **failure to thrive.**

Therefore an **affected female** will transmit the disease to **50% of her sons** and **50% of her daughters.**

An **affected male** will transmit the condition to **all of his daughters** but **none of his sons.**

It is caused by **impaired phosphate reabsorption** in **the renal tubules.**

**Features:**

- **Failure to thrive**
- **NORMAL serum calcium, low phosphate, elevated ALP.**
- X-ray changes: **cupped metaphysis** with **widening of the epiphyses.**

**Diagnosis** is made by demonstrating **increased urinary phosphate.**

**Management:**

- High-dose vitamin D supplements.
- Oral phosphate supplements.

**NB: Oncogenic osteomalacia:**
Certain **tumours** including **mesenchymal** tumours, **adenocarcinoma** (e.g. prostatic carcinoma) and **haematological** malignancies such as **myeloma** and **CLL** appears to produce **phosphaturic substances.**
Patient presents with **bony pain** and /or **fracture, profound proximal myopathy** and **severe hypophosphataemia** usually accompanied by **marked reduction of concentration of 1, 25-OH Vitamin D.**
**Treatment: Vit D metabolites** and **phosphate supplements.**

- It is a neuroendocrine tumours, which originate from **enterochromaffin** cells of the **intestine.**
- Usually occurs when **metastases** are present in the **liver** and release **serotonin (5-HT)** into the **systemic** circulation which will cause **flushing, diarrhoea** and **bronchospasm.**
- They are indolent tumours secreting more than 20 different hormones, likely 5-HT, kinins, prostaglandins and other vasoactive substances are secreted.
- Most of cases with more than **95%** of patients with carcinoid tumour have **liver metastasis** at the time of diagnosis.
- The carcinoid syndrome **only** arises **when liver metastases are present** and the tumour products being metabolised by the liver by draining directly into the hepatic veins.
- May also occur with lung carcinoid as mediators are not 'cleared' by the liver.
- The most common **sites** for the **primary** tumour are the **appendix (40%), terminal ileum (30%), rectum (20%),** and less commonly in the bronchus, ovary and testis.
- 80% of tumours greater than 2 cm in diameter will metastasize.
- **Very bad prognosis: average survival** is **5-10 years from diagnosis**

## Hypokalemia with/without hypertension

For exams it is useful to be able to classify the causes of hypokalaemia in to those associated with hypertension, and those which are not.

### Hypokalaemia with hypertension:

- **Conn's syndrome** (primary hyperaldosteronism)
- **Cushing's syndrome**
- **Liddle's syndrome** (pseudo-hyperaldosteronism)
- **11-beta hydroxylase deficiency***
- **Carbenoxolone**, an anti-ulcer drug
- **Liquorice excess.**
- **Familial glucocorticoid remediable aldosteronism (GRA)**

**NB**: ***21-hydroxylase deficiency,** which accounts for 90% of congenital adrenal hyperplasia cases, is **not** associated with hypertension. It is associated with precocious puberty in boys.

**Liddle's syndrome** is a rare **autosomal dominant** disorder that mimics hyperaldosteronism the so-called **pseudo-hyperaldosteronism.**, that there is **low renin and low aldosterone** resulting in **hypokalaemia** and **alkalosis** associated with hypertension. It is thought to be caused by **disordered Na channels** in the **distal** tubules leading to **increased reabsorption of sodium,** so **serum Na is usually higher.** Treatment is with either **Amiloride** or **triamterene** (**NOT** Aldactone).

Both **liquorice** and **carbenoxolone inhibit 11bHSD (11 beta hydroxyl-steroid dehydrogenase)** and produce **pseudo-hyperaldosteronism** with hypertension and hypokalemia yet appropriately **low renin** and **low aldosterone** concentrations.

**11bHSD** is responsible for the conversion of cortisol to the inactive cortisone, preventing activation of the mineralocorticoid receptor by cortisol but permitting activation by aldosterone.

## Primary hyperaldosteronism:

It is associated with **High BP + high aldosterone, low renin, alkalosis, low potassium, low magnesium** and **normal/high sodium.**

An important differential diagnosis here is **renal artery stenosis (RAS).**

**Causes** of primary hyperaldosteronism include:
1) **Conn's** syndrome (Adrenal **hyperplasia / adenoma**) causes **over 50%.**
2) **Adrenal carcinoma** (rare).
3) **Glucocorticoid deficiency** - also called **glucocorticoid-remediable aldosteronism (GRA).** Note that this is isolated glucocorticoid (cortisol) deficiency driving high ACTH levels and increased aldosterone production. Addison's disease is different as it involves both glucocorticoid and mineralocorticoid deficiencies.

**Screening** for hyperaldosteronism should be considered for:
**1) Hypertensive patients with hypokalemia (not due to treatment),**
**2)** Those **with marked diuretic-induced hypokalemia (<3.0)** and
**3)** Those **with refractory hypertension (failure to respond to ≥ 3 agents).**

Primary hyperaldosteronism was previously believed to account for less than 1% of hypertension, but recent studies have shown **a much higher**

**prevalence (up to 12%)** and have demonstrated that most patients are normokalaemic.

Hypokalaemia in the presence of ACEI and thiazide use is highly suspicious of primary hyperaldosteronism.

Quite marked hypokalaemia (K = 3 mmol/L), even in the presence of ACEI, is a further pointer to the diagnosis.

Primary hyperaldosteronism may therefore be **the most common potentially curable cause of hypertension**, and as such should always be considered.

**The investigation of choice** is **the renin/aldosterone ratio (RAR)**, which will help differentiate between **primary hyperaldosteronism** (**high aldosterone** and **low rennin**) and **renovascular disease** as possible causes (**both** renin and aldosterone will be **high**).

**RAS** usually cause **secondary hyperaldosteronism**.

The renin/aldosterone ratio (RAR), together with cortisol, can be used to diagnose primary hyperaldosteronism when you would expect the **aldosterone to be high**, **renin low** and **normal cortisol**.

If **renovascular disease** is suspected, then angiography or **MRA** is a reasonable approach to investigation, but this may follow aldosterone/renin estimation.

The differential **size** on **renal ultrasound** raises the possibility of **renal artery stenosis (RAS)**, which would result in **elevated both renin and aldosterone levels.**

The **spot aldosterone: renin ratio greater than 800** raises the strong possibility that this man is suffering from hypor-reninaemic hyper-aldosteronism as in RAS.

Whilst addition of further anti-hypertensives may drive his BP closer to goal they are unlikely to be effective and **surgery** is the most appropriate intervention.

Patients ingesting large amounts of sodium, those with renal impairment, or those taking beta-blockers can have **false-positive results**.

Salt-restriction, ACEIs and ARBs, spironolactone and other diuretics can lead to **false-negative results**.

So you should check **plasma renin, aldosterone and cortisol level after washout of antihypertensives for 2 weeks.**

**Alpha-blockers (Doxazosin)** and **CCBs (amlodipine)** are the hypertensives of choice in patients undergoing renin/aldosterone ratio measurements.

**MRI / CT abdomen (Adrenals)** is the investigation that is likely to confirm the possibility of an adrenal adenoma.

**Treatment:**

- Adrenal adenoma >>> **Resection**
- Adrenal hyperplasia >>> **Spironolactone** for many years.
- Glucocorticoid suppressible hyperaldosteronism >>> **Dexamethasone.**

## Familial glucocorticoid remediable aldosteronism (GRA):

Familial GRA is an **autosomal dominant** condition where a mutation leads to **ACTH responsive aldosterone production** from the zona **fasciculata** rather than the zona glomerulosa.

It occurs because the regulatory portion of the 11b-OH gene binds to the aldosterone synthase gene.

The **resistant hypertension, hypokalaemia** and **strong family history** are all pointers to the underlying diagnosis.

**EX:** Young male + resistant HTN + low K + with F/H + **good BP response** after a trial of **hydrocortisone.**

**Current UK guidelines with regard to CKD recommend referral for further investigation of atherosclerotic renal artery stenosis (RAS)** when there is:

1) **Refractory HTN** (BP >150/90 mmHg despite 3 antihypertensive);
2) **Recurrent episodes** of **flash pulmonary oedema despite normal** left ventricular function (LVF).
3) **Rise of >20% serum creatinine** or **fall of GFR >15% over 12 months** with high clinical suspicion of widespread atherosclerosis, **or during the first 2 months after initiation with a ACEIs or ARBs.**

## Hypokalaemia without hypertension:

- **Diuretics**
- **GI loss** (e.g., Diarrhoea, vomiting)
- **RTA (type 1 and 2**)**
- **Bartter's syndrome**
- **Gitelman syndrome**
- **(Thyrotoxic) hypokalaemic periodic paralysis**

**NB**: **Type 4 RTA renal tubular acidosis is associated with **hyperkalaemia** as there is a **hypo-reninaemic hypo-aldosteronism**, which may also be produced with diabetic nephropathy, hence hyperkalaemia and hyponatraemia is more typical.

**Bartter's syndrome** is an inherited cause (usually **autosomal recessive**) of ***severe*** hypokalaemia due to **defective chloride absorption at the Na+ K+ 2Cl- co-transporter** in the ascending loop of Henle Loop diuretics work by inhibiting NKCC2 - think of Bartter's syndrome as like taking large doses of furosemide

It should be noted that it is associated with normotension. It is usually presents in **childhood** with **failure to thrive**, but it can also present in adolescence with polyuria, nocturnal enuresis, polyuria, polydipsia and growth retardation, weakness, and nephrocalcinosis with renal stones are common. No hypomagnesaemia. Urinary Na, K and CL are raised.

Abdominal x-ray showing nephrocalcinosis - a classical finding in type 1 RTA

**Treatment:** is aimed at preventing K wasting, for example with **spironolactone** and electrolyte supplements. **Indomethacin** is also effective, by inhibiting excess prostaglandin synthesis.

**EX:** A 16-year-old male presents with lethargy + low serum K (2.8 mmol/L) + renal stones, otherwise all are normal >>> Bartter's syndrome.

**EX:** A 14-year-old boy is being investigated for **nocturnal enuresis**.

His mother also reports that he is not doing well academically at school and that he is easily fatigued by physical exertion. BP is normal.

Lab: K = **3**, HCO3= **35**, ↑24hrs urinary K = **250** mmol/24 hr (25-100).

The diagnosis: **Bartter's** syndrome (hypokalaemic metabolic alkalosis with urinary potassium wasting).

**Gitelman's syndrome** is due to a defect in the **thiazide-sensitive Na+ Cl- transporter** in **the distal convoluted tubule.** It is associated with hypokalaemia and normotension or low normal BP. Also there is metabolic **alkalosis, hypomagnesaemia** and **hypocalciuria** (low urinary calcium/creatinine ratio). **Treatment: K+ and Mg++ replacement,** if failed **>>> Spironolactone.**

| | BP | Renin | Aldosterone |
|---|---|---|---|
| Conn's syndrome | **HTN** | ↓ | ↑ |
| Liddle's syndrome | **HTN** | ↓ | ↓ |
| RAS | **HTN** | ↑ | ↑ |
| Bartter's syndrome | Normal | ↑ | ↑ |
| Gitelman's syndrome | Normal | ↑ | ↑ |

☺☺ **Little** minded people (**Liddle**) would have HTN, but **gentlemen** (**Gitelman**) would not develop HTN ☺☺

Bartter's syndrome is like Gitleman's in (hypokalaemia, metabolic alkalosis and normotension) but Bartter's is **more severe** and patients therefore present **earlier** in childhood with **profound hypokalaemia** and hypotension with constipation, growth failure, muscle cramps and weakness and ± nephrocalcinosis in **early childhood**.
But in **Gitleman's urinary calcium excretion is low,** and this can also be used as a differentiator.

**Hyperkalaemia and hyponatraemia:**
- Acute hypoadrenalism
- Type IV 4 RTA
- Congestive cardiac failure, hepatic and renal failure.

**Hypokalemia** and **hypernatremia** >>> in **Hyperaldosteronism** either **primary** like Conn's disease or **pseudo-hyperaldosteronism** like:**Liddle's syndrome and others.**

# Alkaline phosphatase

## Causes of raised alkaline phosphatase (ALP)

- liver: cholestasis, hepatitis, fatty liver, neoplasia
- Paget's
- osteomalacia
- bone metastases
- hyperparathyroidism
- renal failure
- physiological: pregnancy, growing children, healing fractures

The table below splits the causes according to the calcium level

| Raised ALP and raised calcium | Raised ALP and low calcium |
|---|---|
| Bone metastases<br>Hyperparathyroidism | Osteomalacia<br>Renal failure |

**Vitamin D** >>> increases **both** plasma **calcium** and plasma **phosphate** levels.

**NB**: The **intestinal absorption** of **calcium** is facilitated by **1, 25 dihydroxy-vitamin D**, which stimulates the microvillous membrane of the enterocyte to synthesise the calcium-binding carrier protein necessary for active calcium ion absorption.
I.e. **there is no direct effect of PTH on GIT regarding ca absorption.**

# Hypophosphataemia

serum phosphate level of less than 2.5 mg/dl (0.8 mmol/L).

## Causes

- alcohol excess
- acute liver failure
- diabetic ketoacidosis
- **refeeding syndrome**
- primary hyperparathyroidism
- osteomalacia

## Consequences

- red blood cell haemolysis
- white blood cell and platelet dysfunction
- muscle weakness and rhabdomyolysis
- central nervous system dysfunction

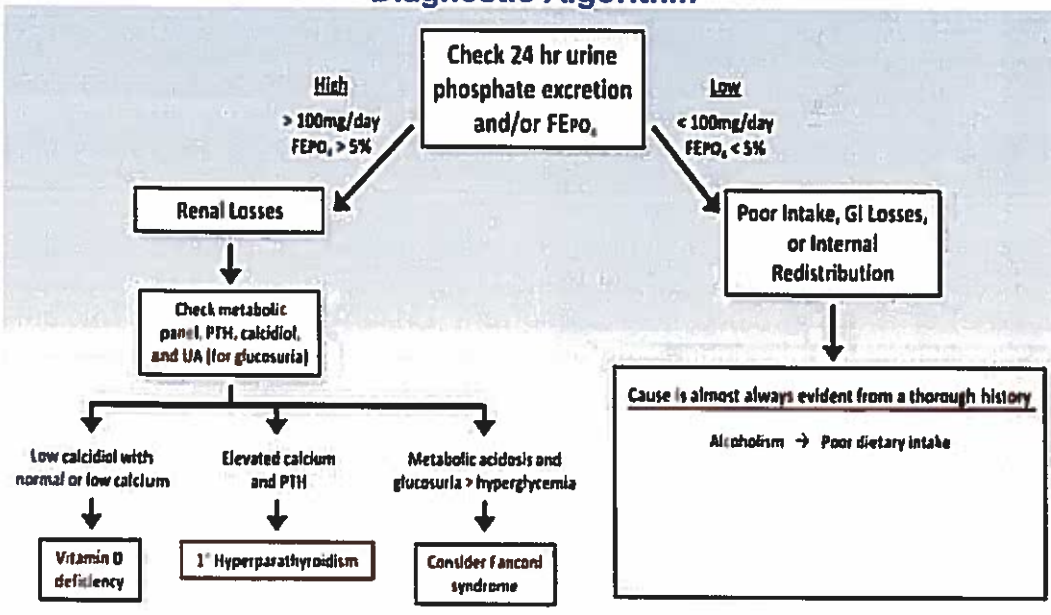
**Fanconi syndrome** is a genetic disorder of the renal proximal tubule whereby various substances-including glucose, bicarbonate, potassium, and phosphate-are unable to be reabsorbed, causing their loss in the urine. It can lead to growth defects and bone disorders.

## Features

- **Cardiac:** arrhythmias
- **Musculoskeletal:** Osteomalacia (fatigue, muscle pain and weakness, respiratory muscle weakness). **severe hypophosphatemia (< 2.5 mg/dl) is associated with elevated serum alkaline phosphatase.**
- **Neurological:** paresthesia, altered mental state, seizures
- **Hematological:** anemia, haemolysis, and thrombocytopenia
- **Impaired immunity** (WBC and platelet dysfunction)
- **Hypophosphatemia** >>↓2,3-diphosphoglycerate (2,3-DPG), (a glycolytic intermediate in red blood cell metabolism that has higher affinity for deoxygenated hemoglobin than for oxygenated hemoglobin) >> ↑ affinity of hemoglobin (Hb) for oxygen >> shifting the dissociation curve to the left >> impairing red blood cell release of oxygen to tissues

Why is hypophosphatemia a problem in patients with respiratory failure?
Limited release of oxygen to tissues because of 2,3-DPG depletion and respiratory muscle weakness.

### Diagnostic Algorithm


Check 24 hr urine phosphate excretion and/or FEPO4
High
> 100mg/day
FEPO4 > 5%
Low
< 100mg/day
FEPO4 < 5%
Renal Losses
Poor Intake, GI Losses, or Internal Redistribution
Check metabolic panel, PTH, calcidiol, and UA (for glucosuria)
Cause is almost always evident from a thorough history
Alcoholism → Poor dietary intake
Low calcidiol with normal or low calcium
Elevated calcium and PTH
Metabolic acidosis and glucosuria > hyperglycemia
Vitamin D deficiency
1° Hyperparathyroidism
Consider Fanconi syndrome

**MRCPUK part 1 exam: what is the mechanism of Hypophosphataemia during treatment of DKA?**
**>> Shift from extracellular to intracellular space**

**MRCPUK part 1 exam: what is the mechanism of Hypophosphataemia in alcoholic patients after hospital admission?**

>> Shift from extracellular to intracellular space. The alcoholic patient often has chronic phosphate depletion, and, after admission to the hospital, is prone to severe hypophosphatemia resulting from redistribution of extracellular phosphate into the cells.

- **Two factors may contribute to this shift:**
  1) I.V therapy with dextrose-containing solutions or refeeding >> ↑ Glucose >> ↑insulin release >> ↑ phosphate uptake by the cells
  2) alcohol withdrawal >> hyperventilation >> acute respiratory alkalosis >> intracellular alkalosis >> stimulates intracellular phosphofructokinase >> ↑ glycolysis -> movement of phosphate into cells.

## Hyponatraemia

**Hyponatraemia** (based on europian endocrinology, icu and europian society of nephrology guidline on hyponatremia 2014 and latest review of medscape 2022)

**Hyponatraemia** is a clinical feature in 15–20% of emergency admissions to hospital. It is associated with increased mortality, morbidity and length of hospital stay in patients presenting with a range of conditions. Hyponatraemia is therefore both common and important

**Hyponatraemia** may be caused by water excess or sodium depletion. Causes of pseudohyponatraemia include hyperlipidaemia (increase in serum volume) or a taking blood from a drip arm. Urinary sodium and osmolarity levels aid making a diagnosis

### Classifications

**based on severity:**

- Mild hyponatraemia: serum sodium between 130 and 135 mmol/1
- Moderate hyponatraemia: serum sodium between 125 and 129 mmol/1
- Profound hyponatraemia: serum sodium < 125 mmol/1

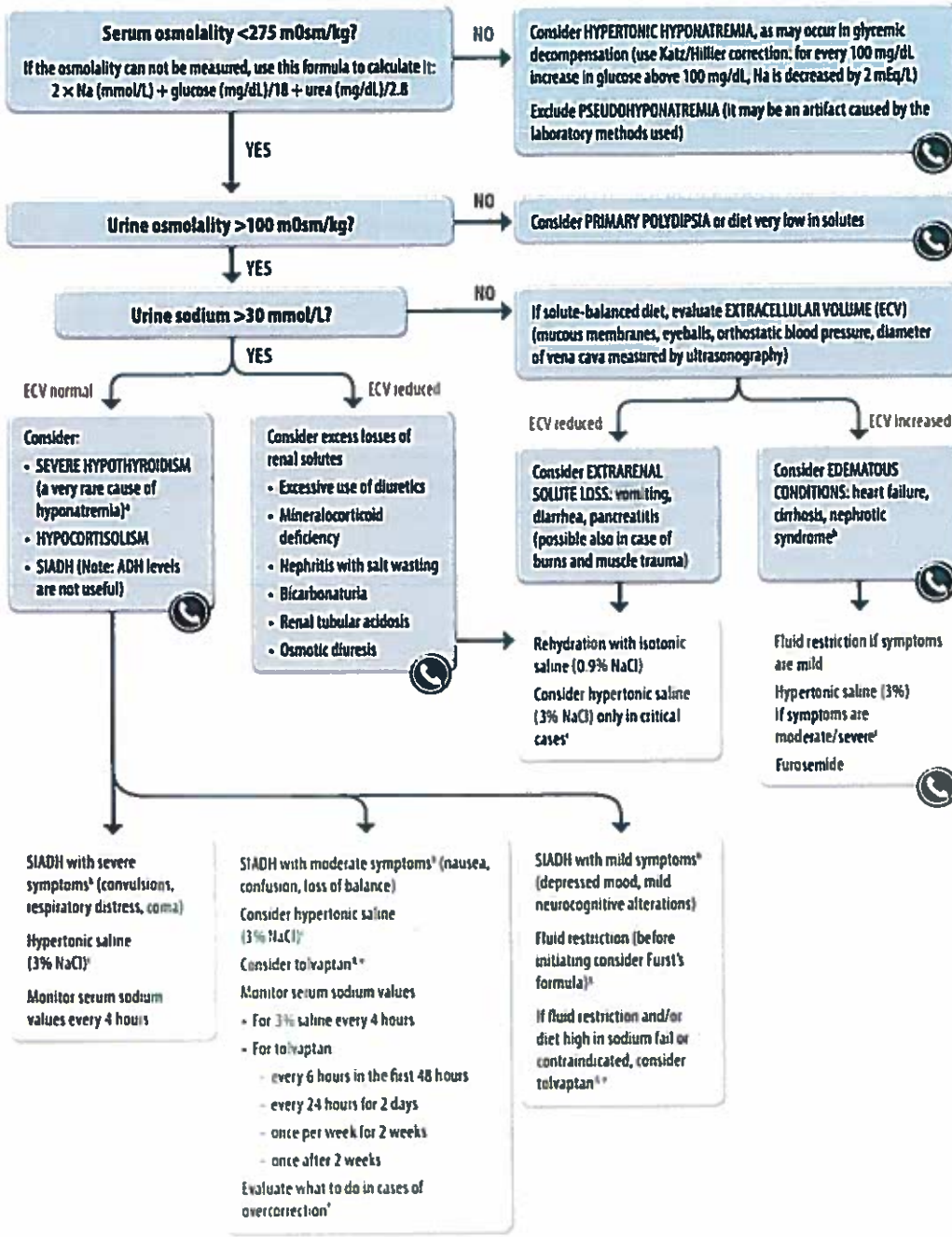
**based on time of development:**

- Acute hyponatraemia: hyponatraemia that is documented to exist < 48h.
- Chronic hyponatraemia: hyponatraemia that is documented to exist ≥ 48h.
  - If hyponatraemia cannot be classified, we consider it being chronic

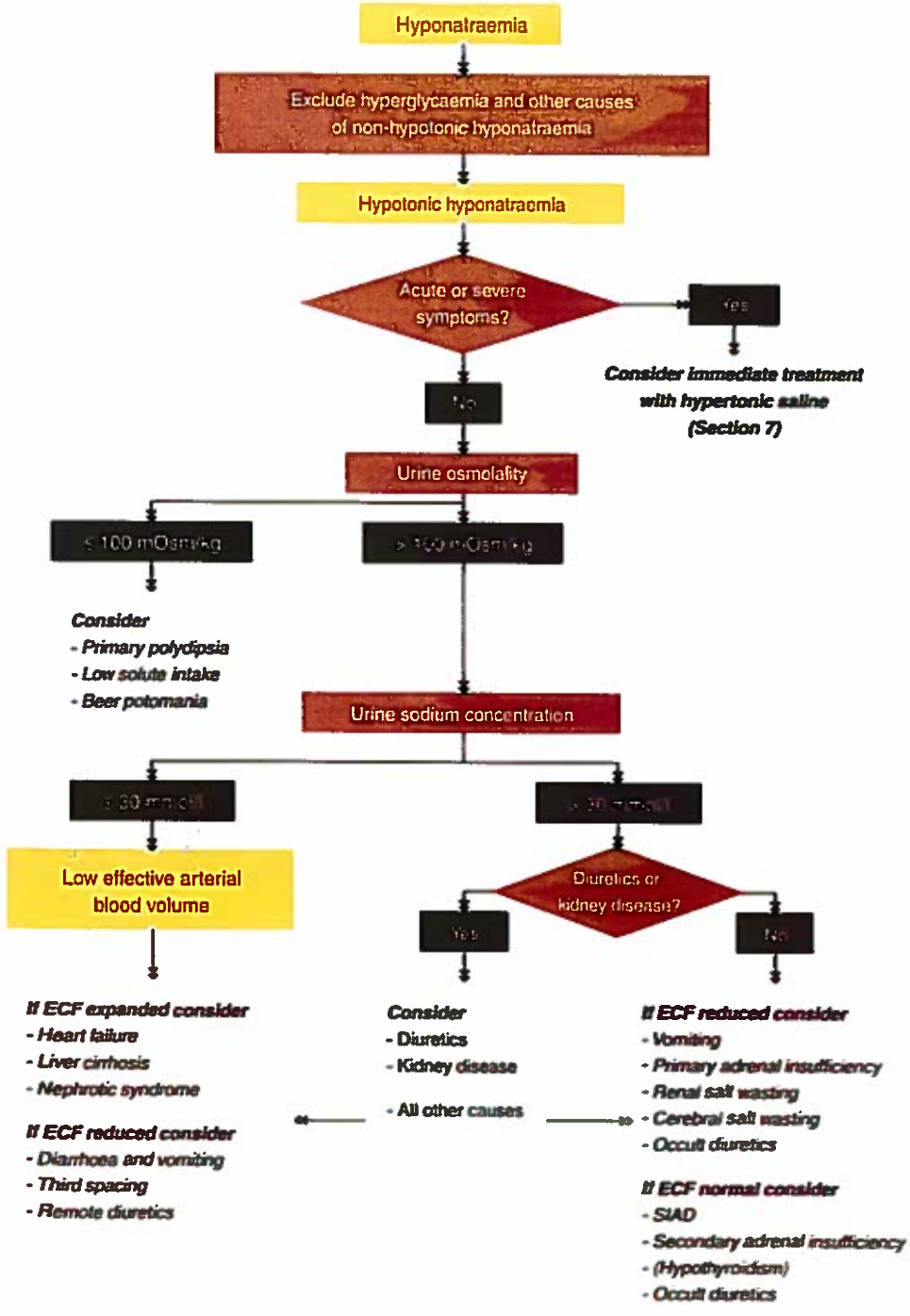
## Mechanisms of causes

- water excess
- sodium depletion
- Pseudohyponatraemia: (isotonic hyponatraemia)
  - Causes
    - Hyperglycaemia
    - hyperlipidaemia (increase in serum volume)
    - hyperproteinemia (e.g. myeloma)
    - taking blood from a drip arm.
  - exclude hyperglycaemic hyponatraemia by measuring the corrected serum Na+
    - adding 2.4mmol/1 to the measured serum sodium for every 5.5mmol/l incremental rise rn serum glucose concentration above a standard serum glucose concentration of 5.5mmol/l.
    - corrected Na+= measured Na++ 2.4 x (serum glucose mmol - 5.5/5.5mmol)
  - Non-hypotonic hyponatraemia does not cause brain oedema and is managed differently from hypotonic hyponatraemia.

## Algorithm for diagnosis and management of hyponatremia


Serum osmolality <275 mOsm/kg?
If the osmolality can not be measured, use this formula to calculate it: 2 × Na (mmol/L) + glucose (mg/dL)/18 + urea (mg/dL)/2.8
NO
Consider HYPERTONIC HYPONATREMIA, as may occur in glycemic decompensation (use Katz/Hillier correction: for every 100 mg/dL increase in glucose above 100 mg/dL, Na is decreased by 2 mEq/L)
Exclude PSEUDOHYPONATREMIA (it may be an artifact caused by the laboratory methods used)
YES
Urine osmolality >100 mOsm/kg?
NO
Consider PRIMARY POLYDIPSIA or diet very low in solutes
YES
Urine sodium >30 mmol/L?
NO
If solute-balanced diet, evaluate EXTRACELLULAR VOLUME (ECV) (mucous membranes, eyeballs, orthostatic blood pressure, diameter of vena cava measured by ultrasonography)
YES
ECV normal
ECV reduced
Consider:
• SEVERE HYPOTHYROIDISM (a very rare cause of hyponatremia)a
• HYPOCORTISOLISM
• SIADH (Note: ADH levels are not useful)
Consider excess losses of renal solutes
• Excessive use of diuretics
• Mineralocorticoid deficiency
• Nephritis with salt wasting
• Bicarbonaturia
• Renal tubular acidosis
• Osmotic diuresis
ECV reduced
ECV increased
Consider EXTRARENAL SOLUTE LOSS: vomiting, diarrhea, pancreatitis (possible also in case of burns and muscle trauma)
Consider EDEMATOUS CONDITIONS: heart failure, cirrhosis, nephrotic syndromeb
Rehydration with isotonic saline (0.9% NaCl)
Consider hypertonic saline (3% NaCl) only in critical cases[c]
Fluid restriction if symptoms are mild
Hypertonic saline (3%) if symptoms are moderate/severe[c]
Furosemide
SIADH with severe symptoms[b] (convulsions, respiratory distress, coma)
Hypertonic saline (3% NaCl)[c]
Monitor serum sodium values every 4 hours
SIADH with moderate symptoms[b] (nausea, confusion, loss of balance)
Consider hypertonic saline (3% NaCl)[c]
Consider tolvaptan[d,e]
Monitor serum sodium values
• For 3% saline every 4 hours
• For tolvaptan
– every 6 hours in the first 48 hours
– every 24 hours for 2 days
– once per week for 2 weeks
– once after 2 weeks
Evaluate what to do in cases of overcorrection[c]
SIADH with mild symptoms[a] (depressed mood, mild neurocognitive alterations)
Fluid restriction (before initiating consider Furst's formula)[a]
If fluid restriction and/or diet high in sodium fail or contraindicated, consider tolvaptan[d,e]

## Algorithm for the diagnosis of hyponatraemia




https://academic.oup.com/ndt/article/29/suppl_2/i1/1904943 by guest on 07 August 2022

## Urinary sodium > 30 mmol/l

=Sodium depletion, renal loss

**patient often hypovolaemic:**

- diuretics: **thiazides**, loop diuretics
- **Addison's disease**
- diuretic stage of renal failure

**Patient often euvolaemic.**

- SIADH (urine osmolality > 500 mmol/kg)
- **Hypothyroidism**

## Urinary sodium < 30 mmol/l

=Sodium depletion, extra-renal loss

**Patient dehydrated**

- **diarrhoea, vomiting**, sweating
- **burns, adenoma of rectum**

**Water excess (patient often hypervolaemic and oedematous)**

- secondary hyperaldosteronism: **heart failure, liver cirrhosis**
- nephrotic syndrome
- IV dextrose
- psychogenic polydipsia

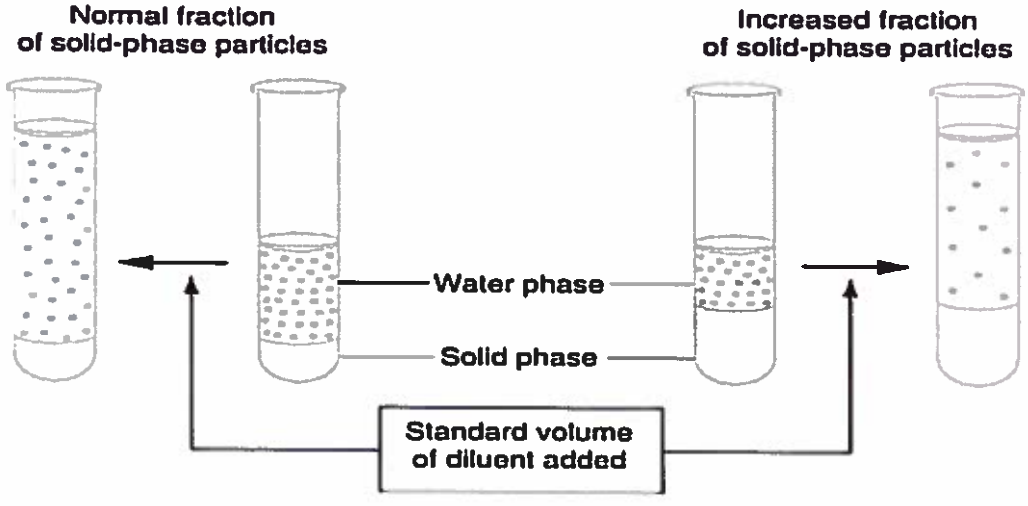
Association between serum glucose concentration, measured serum sodium and corrected serum sodium concentration. Calculated using equation from Hillier TA, Abbott RD & Barrett EJ. Hyponatremia: evaluating the correction factor for hyperglycemia.

| | Measured (glucose) (mg/dl) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | True (Na+) (mmol/l) | | | | | | | |
| Measured (Na+) (mmol/l) | 100 | 200 | 300 | 400 | 500 | 600 | 700 | 800 |
| 135 | 135 | 137 | 140 | 142 | 145 | 147 | 149 | 152 |
| 130 | 130 | 132 | 135 | 137 | 140 | 142 | 144 | 147 |
| 125 | 125 | 127 | 130 | 132 | 135 | 137 | 139 | 142 |
| 120 | 120 | 122 | 125 | 127 | 130 | 132 | 134 | 137 |
| 115 | 115 | 117 | 120 | 122 | 125 | 127 | 129 | 132 |
| 110 | 110 | 112 | 115 | 117 | 120 | 122 | 124 | 127 |
| 105 | 105 | 107 | 110 | 112 | 115 | 117 | 119 | 122 |
| 100 | 100 | 102 | 105 | 107 | 110 | 112 | 114 | 117 |
| 95 | 95 | 97 | 100 | 102 | 105 | 107 | 109 | 112 |
| 90 | 90 | 92 | 95 | 97 | 100 | 102 | 104 | 107 |
| 85 | 85 | 87 | 90 | 92 | 95 | 97 | 99 | 102 |
| 80 | 80 | 82 | 85 | 87 | 90 | 92 | 94 | 97 |
| 75 | 75 | 77 | 80 | 82 | 85 | 87 | 89 | 92 |
| 70 | 70 | 72 | 75 | 77 | 80 | 82 | 84 | 87 |

**Causes of non-hypotonic hyponatraemia.**

| Setting | Serum osmolality | Examples |
|---|---|---|
| Presence of 'effective' osmoles that raise serum osmolality and can cause hyponatraemia | Isotonic or hypertonic | Glucose [31] Mannitol [32] Glycine [33] Histidine–tryptophan–ketoglutarate [243] |
| Presence of 'ineffective' osmoles that raise serum osmolality but do not cause hyponatraemia | Isotonic or hyperosmolar | Hyperosmolar radiocontrast media [244] Maltose [245] Urea [36] Alcohols [36] Ethylene glycol [36] |
| Presence of endogenous solutes that cause pseudohyponatraemia (laboratory artifact) | Isotonic | Triglycerides [97], cholesterol [97] and protein Intravenous immunoglobulins [96] Monoclonal gammapathies [246] |

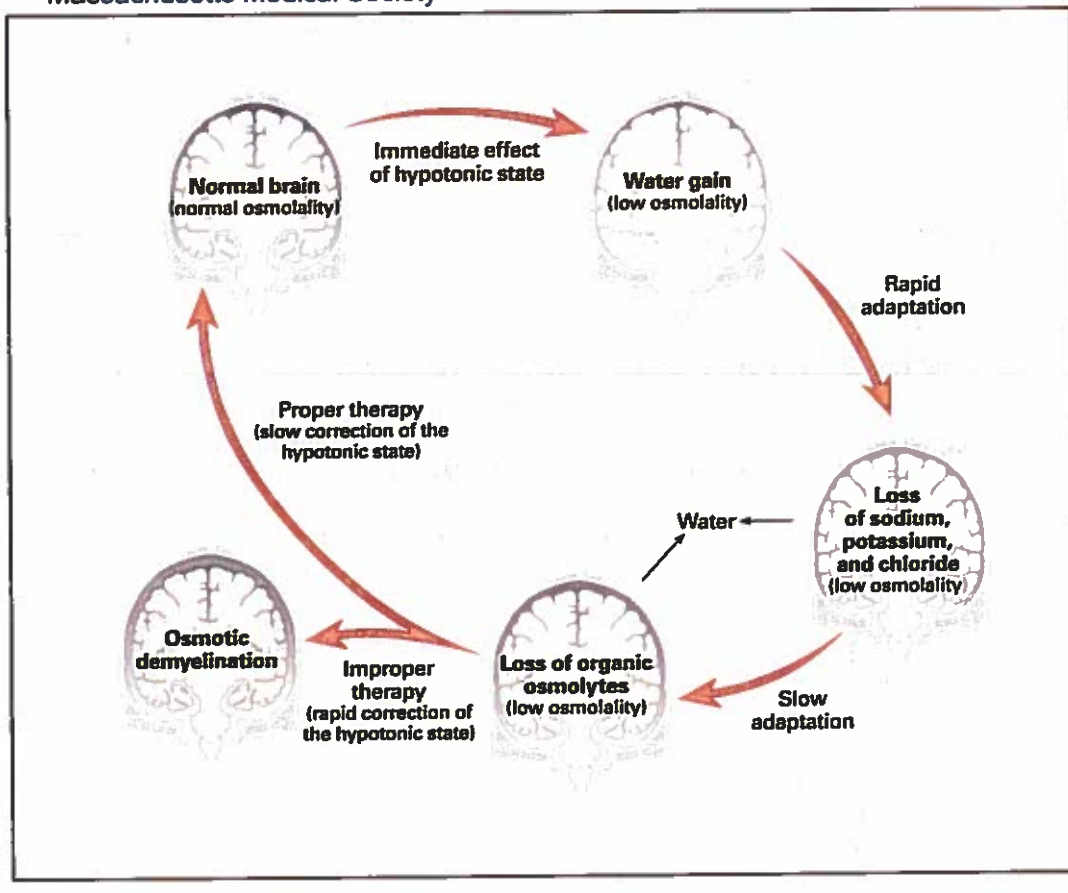
Pseudohyponatraemia. Normally, serum contains 7% solids by volume. In order to reduce the volume of blood needed for analysis, serum is frequently diluted before the actual measurement is obtained. The same volume of diluent is always used; the degree of dilution is estimated under the assumption that the serum contains 7% solid-phase particles. When the fraction of solid-phase particles is increased, the same amount of diluent results in a greater dilution, unbeknownst to the laboratory personnel (right side of figure). Consequently, the calculation of an ion level with the use of a degree of dilution that is based on the incorrect fraction of solid-phase particles will lead to an underestimate.



## Management

- Untreated, severe hyponatraemia may result in **cerebral oedema**, which in turn can cause brain herniation.
- It is therefore important to promptly identify and treat hyponatremia appropriately. However, the particular management for each patient is based on a number of factors listed below.
- Further to this, over-rapid correction may result in osmotic demyelination syndrome.

Adaptation of the brain to hypotonicity. Reproduced with permission from Massachusetts Medical Society




## Principles

**Management of hyponatremia is complicated and primarily based on the following parameters:**

- **duration of hyponatremia:** is it acute or chronic?
  - **acute:** develops over a period of < 48 hours
  - **chronic:** develops over a period > 48 hours

- **severity of hyponatremia:** what is the sodium level?
  - **mild:** 130-134 mmol/L
  - **moderate**: 120-129 mmol/L
  - **severe**: < 120 mmol/L
- **symptoms:** is the patient symptomatic?
  - patients with mild hyponatraemia may be asymptomatic
  - early symptoms may include: headache, lethargy, nausea, vomiting, dizziness, confusion, and muscle cramps
  - late symptoms may include: seizures, coma, and respiratory arrest
- **the suspected aetiology of the hyponatraemia:**
  - **hypovolemic hyponatraemia/clinically dehydrated:** diuretic stage of renal failure, diuretics, Addisonian crisis.
  - **euvolemic hyponatraemia:** SIADH(clinically euovolemic but in fact slightly overloaded) and hypothyroidism.
  - **hypervolaemic hyponatraemia**: heart failure, liver failure, nephrotic syndrome

## Management

### Initial steps in all patients.

- exclude a spurious result (e.g. blood taken from a drip arm)
- review medications that may cause hyponatraemia

**A. Chronic hyponatremia with moderately severe symptoms:**

start prompt diagnostic assessment.

1) Stop, if possible, medications and other factors that can contribute to or provoke hyponatremia and start cause-specific treatment.
2) **start immediate treatment with a single I.V. infusion of 150 ml 3% hypertonic saline or equivalent over 20 min. aiming for a 5 mmol/l increase in serum sodium concentration.**
3) **the increase in serum sodium concentration must be limited to 10 mmol/l in the first 24 h and 8 mmol/l during every 24 h thereafter, until a serum sodium concentration of 130 mmol/l is reached.**
4) We suggest checking the serum sodium concentration after 1, 6 and 12 h.
5) additional diagnostic exploration for other causes of the symptoms if the symptoms do not improve with an increase in serum sodium concentration must be carried out.
6) We suggest considering to manage the patient as in severely symptomatic hyponatremia if the serum sodium concentration further decreases despite treating the underlying diagnosis.

### B. Acute hyponatremia moderately severe symptoms:

1) Make sure that the serum sodium concentration has been measured using the same technique used for the previous measurement and that no administrative errors in sample handling have occurred.
2) If possible, stop fluids, medications and other factors that can contribute to or provoke hyponatremia (not graded).
3) We recommend starting prompt diagnostic assessment.
4) We recommend cause-specific treatment.
5) **If the acute decrease in serum sodium concentration exceeds 10 mmol/l, we suggest a single I.V infusion of 150 ml 3% hypertonic saline or equivalent over 20 min.**

**If a hypovolemic cause is suspected:**

- normal, i.e., isotonic, saline (0.9% NaCl)
- this may sometimes be given as a trial
  - if the serum sodium rises this supports a diagnosis of hypovolemic hyponatremia
    - if the serum sodium falls an alternative diagnosis such as SIADH is likely

**If a euvolemic cause is suspected:**

- fluid restrict to 500–1000 mL/day
- consider medications:
  - demeclocycline
  - vaptans (see below)

**If a hypervolemic cause is suspected:**

- fluid restrict to 500–1000 mL/day
- consider loop diuretics
- consider vaptans

## Acute hyponatremia with severe symptoms

Patients with acute, severe (<120 mmol/L) or symptomatic hyponatraemia require close monitoring, preferably in an HDU or above setting. **Hypertonic saline (typically 3% NaCl)** is used to correct the sodium level more quickly than would be done in patients with chronic hyponatraemia.

### First-hour management (For frontline physicians)

1. Regardless of whether hyponatremia is acute or chronic prompt i.v. infusion of 150 ml 3% hypertonic over 20 min. followed by checking the serum sodium concentration after 20 min while repeating an infusion of 150 ml 3% hypertonic saline for the next 20 min . the guidelines recommendation is to repeat this twice or until a target of 5 mmol/l increase in serum sodium concentration is achieved.

2. Manage patients with severely symptomatic hyponatremia in an environment where close biochemical and clinical monitoring can be provided
3. Follow-up management in case of improvement of symptoms after a 5 mmol/l increase in serum sodium concentration in the first hour, regardless of whether hyponatraemia is acute or chronic.
4. We recommend stopping the infusion of hypertonic saline.
5. We recommend keeping the i.v. line open by infusing the smallest feasible volume of 0.9% saline until cause-specific treatment is started.
6. We recommend starting a diagnosis-specific treatment if available, aiming at least to stabilise sodium concentration.
7. We recommend limiting the increase in serum sodium concentration to a total of 10 mmol/l during the first 24 h.
8. An additional 8 mmol/l during every 24 h thereafter until the serum sodium concentration reaches 130 mmol/l.
9. We suggest checking the serum sodium concentration after 6 and 12 h and daily afterwards until the serum sodium concentration has stabilised under stable treatment.
10. Follow-up management in case of no improvement of symptoms after a 5 mmol/l increase in serum sodium concentration in the first hour, regardless of whether hyponatraemia is acute or chronic. **We recommend continuing an I.V. infusion of 3% hypertonic saline or equivalent aiming for an additional 1 mmol/l per hr.** (USUALLY BY INFUSING 1mL/Kg/hr) increase in serum sodium concentration AND stopping the infusion of 3% hypertonic saline or equivalent when the symptoms improve, the serum sodium concentration increases 10 mmol/l in total or the serum sodium concentration reaches 130 mmol/l, whichever occurs first.
11. We recommend additional diagnostic exploration for other causes of the symptoms than hyponatremia .
12. We suggest checking the serum sodium concentration every 4 h as long as an i.v. infusion of 3% hypertonic saline or equivalent is continued. **Advice for clinical practice** •

Prompt infusion of hypertonic saline may save lives. Do not expect patients with severe symptoms to completely recover immediately, as it may take some time for the brain to fully recover. Be aware that sometimes it may not be possible to assess an improvement in symptoms, e.g. because the patient is intubated and sedated. In these cases, we advise to follow guidance. • Keep in mind that if hypokalaemia is present, correction of the hypokalaemia will contribute to an increase in serum sodium concentration. • To achieve the 1

mmol/l per h increase advised the formula of Adrogué–Madias may be used, but keep in mind that the actual increase may exceed the calculated increase change in serum Na.

### What to do if hyponatraemia is corrected too rapidly

prompt intervention for relowering the serum sodium concentration MUST BE carried out if it increases >10 mmol/l during the first 24 h or >8 mmol/l in any 24 h thereafter .

1) discontinue the ongoing active treatment.
2) consult an expert to discuss if it is appropriate to start an infusion of 10 ml/kg body weight of electrolyte-free water (e.g. glucose solutions) over 1 h under strict monitoring of urine output and fluid balance.
3) consult an expert to discuss if it is appropriate to add i.v. desmopressin 2 µg, with the understanding that this should not be repeated more frequently than every 8 hrs.

## Notes on specific medications

### Vasopressin/ADH receptor antagonists (vaptans):

these act primarily on V2 receptors - antagonism of V2 receptors results in selective water diuresis, sparing the electrolytes.

- They should be avoided in patients who have hypovolemic hyponatremia
- Vasopression/ADH receptor antagonists can stimulate the **thirst** receptors leading to the desire to drink free water. They can be **hepatotoxic** in patients with underlying liver disease.

## Complications of treatment

Osmotic demyelination syndrome (central pontine myelinolysis)

- can occur due to over-correction of severe hyponatremia
- to avoid this, Na+ levels are only raised by 4 to 6 mmol/l in a 24-hour period
- symptoms usually occur after 2 days and are usually irreversible: dysarthria, dysphagia, paraparesis or quadriparesis, seizures, confusion, and coma
- patients are awake but are unable to move or verbally communicate, also called **'Locked-in syndrome'**

## Hyperkalaemia

Plasma potassium levels are regulated by a number of factors including aldosterone, acid-base balance and insulin levels. Metabolic acidosis is associated with hyperkalaemia as hydrogen and potassium ions compete with each other for exchange with sodium ions across cell membranes and in the distal tubule. ECG changes seen in hyperkalaemia include tall-tented T waves, small P waves, widened QRS leading to a sinusoidal pattern and asystole

### Causes of hyperkalaemia:

- acute kidney injury
- drugs*: potassium sparing diuretics, **ACE inhibitors, angiotensin 2 receptor blockers,** spironolactone, **ciclosporin, heparin****
- **metabolic acidosis**
- **Addison's disease**
- **rhabdomyolysis**
- **massive blood transfusion**

### Foods that are high in potassium:

- salt substitutes (i.e. Contain potassium rather than sodium)
- bananas, oranges, kiwi fruit, avocado, spinach, tomatoes

*beta-blockers interfere with potassium transport into cells and can potentially cause hyperkalaemia in renal failure patients - remember beta-agonists, e.g. Salbutamol, are sometimes used as emergency treatment

**both unfractionated and low-molecular weight heparin can cause hyperkalaemia. This is thought to be caused by inhibition of aldosterone secretion

## Hypokalaemia

Potassium and hydrogen can be thought of as competitors. Hyperkalaemia tends to be associated with acidosis because as potassium levels rise fewer hydrogen ions can enter the cells

### Hypokalaemia with alkalosis

- vomiting
- **thiazide** and loop diuretics
- **Cushing's syndrome**
- Conn's syndrome (primary hyperaldosteronism)

### Hypokalaemia with acidosis

- diarrhoea
- renal tubular acidosis
- acetazolamide
- partially treated diabetic ketoacidosis

Magnesium deficiency may also cause hypokalaemia. In such cases, normalizing the potassium level may be difficult until the magnesium deficiency has been corrected

## Pseudohypoparathyroidism

Pseudohypoparathyroidism is caused by target cell insensitivity to parathyroid hormone (PTH) due to a mutation in a G-protein. In type I pseudohypoparathyroidism
there is a complete receptor defect whereas in type II the cell receptor is intact. Pseudohypoparathyroidism is typically inherited in an autosomal dominant fashion*

### Bloods

- PTH: high
- calcium: low
- phosphate: high

### Features

- short fourth and fifth metacarpals
- short stature
- cognitive impairment
- obesity
- round face

### Investigation

- infusion of PTH followed by measurement of urinary phosphate and cAMP measurement - this can help differentiate between type I (neither phosphate or cAMP levels rise) and II (cAMP rises but phosphate levels do not change)

*it was previously thought to be an X-linked dominant condition

## Pseudohyperkalaemia

Pseudohyperkalaemia is a rise in serum potassium that occurs due to excessive leakage of potassium from cells, during or after blood is taken. It is a laboratory artefact and does not represent the true serum potassium concentration. The majority of potassium is intracellular and thus leakage from cells can significantly impact serum levels. In this case the potassium is released as the large numbers of platelets aggregate and degranulate.

### Causes include:

- haemolysis during venipuncture (excessive vacuum of blood drawing, prolonged tourniquet use or too fine a needle gauge)
- delay in the processing of the blood specimen
- abnormally high numbers of platelets, leukocytes, or erythrocytes (such as myeloproliferative disorders)
- familial causes

Measuring an arterial blood gas will give a quick and accurate measure of true serum potassium. For obtaining a lab sample, using a lithium heparin tube, requesting a slow spin (on the lab centrifuge) and walking the sample to the lab should ensure an accurate result.

## Bartter's syndrome

Bartter's syndrome is an inherited cause (usually autosomal recessive) of severe hypokalaemia due to defective chloride absorption at the **$Na^+$ $K^+$ 2Cl- cotransporter (NKCC2) in the ascending loop of Henle**. It should be noted that it is associated with **normotension** (unlike other endocrine causes of hypokalaemia such as Conn's, Cushing's and Liddle's syndrome which are associated with hypertension).

Loop diuretics work by inhibiting NKCC2 - think of Bartter's syndrome as like taking large doses of furosemide

### Features

- usually presents in childhood, e.g. Failure to thrive
- polyuria, polydipsia
- hypokalaemia
- **normotension**
- weakness

## Gitelman's syndrome

Gitelman's syndrome is due to a **defect in the thiazide-sensitive $Na^+$ $Cl^-$ transporter in the distal convoluted tubule.**

### Features

- **normotension**
- **hypokalaemia**
- **hypocalciuria**
- hypomagnesaemia
- metabolic alkalosis

## Liddle's syndrome

Liddle's syndrome is a rare autosomal dominant condition that causes hypertension and hypokalaemic alkalosis. It is thought to be caused by disordered sodium channels in the distal tubules leading to increased reabsorption of sodium.

**Treatment is with either amiloride or triamterene**

## Hypernatraemia

### Causes of hypernatraemia

- dehydration
- osmotic diuresis e.g. hyperosmolar non-ketotic diabetic coma
- diabetes insipidus
- excess IV saline

Hypernatraemia should be corrected with great caution. Although brain tissue can lose sodium and potassium rapidly, lowering of other osmolytes (and importantly water) occurs at a slower rate, predisposing to cerebral oedema, resulting in seizures, coma and death1. Although there are no clinical guidelines by NICE or Royal College of Physicians at present, it is generally accepted that a rate of no greater than 0.5 mmol/hour correction is appropriate[1].

1. Reynolds RM, Padfield PL, Seckl JR; Disorders of sodium balance. BMJ.

# Renal tubular acidosis

All three types of renal tubular acidosis (RTA) are associated with hyperchloraemic metabolic acidosis (normal anion gap).

## Type 1 RTA (distal)

- inability to generate acid urine (secrete H+) in distal tubule
- causes hypokalaemia
- complications include nephrocalcinosis and renal stones
- causes include idiopathic, rheumatoid arthritis, SLE, Sjogren's, amphotericin B toxicity, analgesic nephropathy

**Abdominal x-ray showing** nephrocalcinosis - a classical finding in type 1 RTA

## Type 2 RTA (proximal)

- decreased HCO3- reabsorption in proximal tubule
- causes hypokalaemia
- complications include osteomalacia
- causes include idiopathic, as part of Fanconi syndrome, Wilson's disease, cystinosis, outdated tetracyclines, carbonic anhydrase inhibitors (acetazolamide, topiramate)

## Type 3 RTA (mixed)

- extremely rare
- caused by carbonic anhydrase II deficiency
- results in hypokalaemia

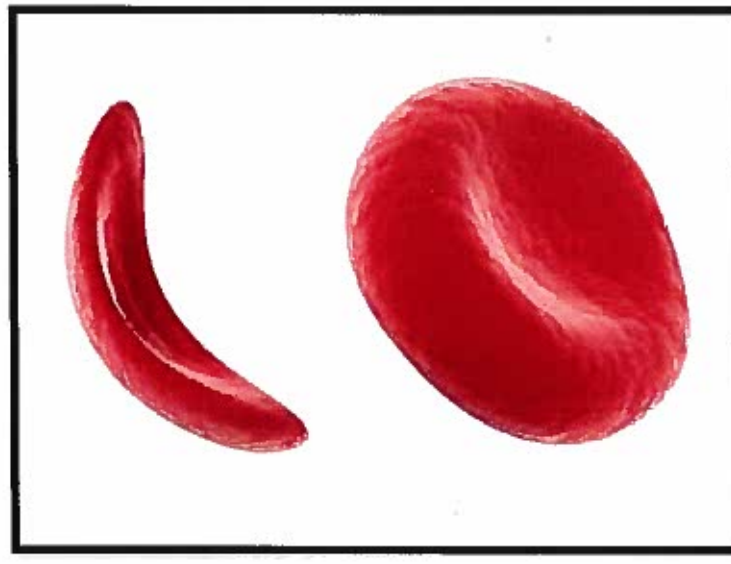
## Type 4 RTA (hyperkalaemic)

- reduction in aldosterone leads in turn to a reduction in proximal tubular ammonium excretion
- causes hyperkalaemia
- causes include hypoaldosteronism, diabetes

## Summary of common workup of common endocrine disorders

| Disorder | Investigation of choice |
|---|---|
| Cushing's | Overnight Dexamethasone Suppression Test Or 24 hours urinary free cortisol |
| Cushing's vs. Pseudo-Cushing's | Insulin Stress Test |
| Addison's | Short Synacthen Test |
| Phaeochromocytoma | Three 24 Hrs. Urinary Catecholamines |
| Acromegaly | OGTT (Oral Glucose Tolerance Test) |
| Carcinoid syndrome | Urinary 5-HIAAA |

# Haematology & Oncology



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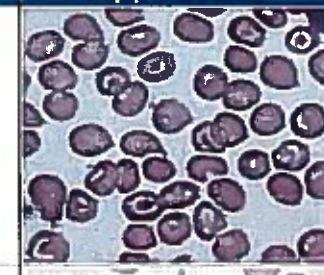
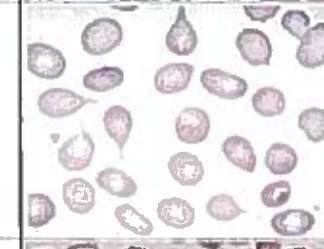
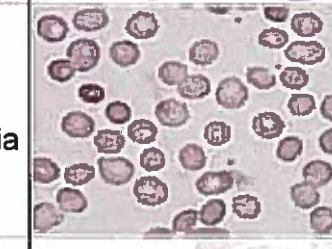
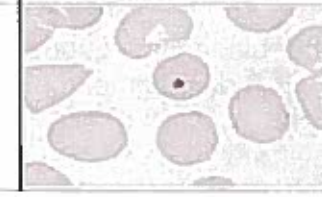
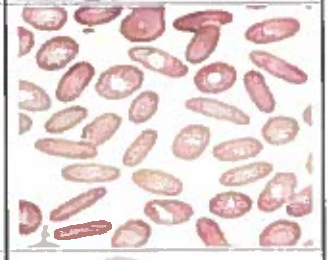
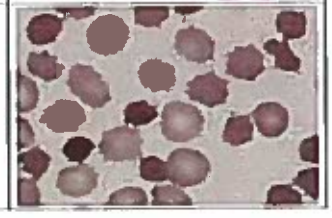
# Important hematological principles

## Blood films:

### pathological cell forms

| Abnormality | Associated condition(s) | Appearance |
|---|---|---|
| Target cells | **Sickle-cell/thalassaemia**<br>**Iron-deficiency anaemia**<br>**Hyposplenism**<br>**Liver disease** |  |
| 'Tear-drop' poikilocytes | **Myelofibrosis** |  |
| Spherocytes | Hereditary spherocytosis<br>Autoimmune hemolytic anaemia |  |
| Basophilic stippling | **Lead poisoning**<br>**Thalassaemia**<br>Sideroblastic anaemia<br>Myelodysplasia | |
| Howell-Jolly bodies | Hyposplenism |  |

| Abnormality | Associated condition(s) | Appearance |
|---|---|---|
| Heinz bodies | **G6PD deficiency**<br>**Alpha-thalassaemia** | |
| Schistocytes ('helmet cells') | **Intravascular haemolysis**<br>**Mechanical heart valve**<br>Disseminated intravascular coagulation | |
| 'Pencil' poikilocytes | **Iron deficency anaemia** |  |
| Burr cells (echinocytes) | Uraemia<br>Pyruvate kinase deficiency | |
| Acanthocytes | Abetalipoproteinemia |  |

Other blood film abnormalities:

- hypersegmented neutrophils: **megaloblastic anaemia**

# Blood products

## Whole blood fractions

| Fraction | Key points |
|---|---|
| Packed red cells | • Used for transfusion in chronic anaemia and cases where infusion of large volumes of fluid may result in cardiovascular compromise.<br>• Product obtained by centrifugation of whole blood.<br>• In a stable patient, red cell packs may be transfused over 90-120 minutes<br>  o Rapid infusion of red cells or fresh frozen plasma may be required in an acutely bleeding patient but not in patient who is stable. |
| Platelet rich plasma | • Usually administered to patients who are thrombocytopaenic and are bleeding or require surgery.<br>• It is obtained by **low speed** centrifugation. |
| Platelet concentrate | • Prepared by **high speed** centrifugation<br>• administered to patients with thrombocytopaenia.<br>• the life span of transfused platelets is only 3-7 days.<br>• platelet transfusion should not take more than 20-30 minutes.<br>• Patients who are refractory to platelet transfusions:<br>  o should be first investigated to check for adequate platelet rises. This is best done on a one or two-hour post platelet transfusion sample.<br>  o Further test would include checking for HLA antibodies |
| Fresh frozen plasma | • Prepared from single units of blood.<br>• Contains clotting factors, albumin and immunoglobulin.<br>• Unit is usually 200 to 250ml.<br>• Usually used in correcting clotting deficiencies in patients with hepatic synthetic failure who are due to undergo surgery.<br>• Usual dose is 12-15ml/$Kg^{-1}$.<br>• It should not be used as first line therapy for hypovolaemia. |
| Cryoprecipitate | • Formed from supernatant of FFP.<br>• Rich source of Factor VIII and fibrinogen.<br>• Allows large concentration of factor VIII to be administered in small volume. |
| SAG-Mannitol Blood | Removal of all plasma from a blood unit and substitution with:<br>• Sodium chloride<br>• Adenine<br>• Anhydrous glucose<br>• Mannitol<br>Up to 4 units of SAG M Blood may be administered. Thereafter whole blood is preferred. After 8 units, clotting factors and platelets should be considered. |

## Hematological changes during pregnancy

### Platelet

- **Isolated thrombocytopenia**
  - **occur in 8%**
  - Usually mild with platelet above 70
  - Occur due to presence **IgG antibodies**, which are reactive to platelet
  - **No intervention** - recover after delivery

### Hypercoagulable state

- ↑ clotting factors
- result of venous stasis secondary to uterine pressure on great veins of lower extremity

### Anemia

- ↑ plasma volume by 50%
- RBC mass only ↑ by 30%
- Result is a dilutional gap of 15-20%

### Leukocytosis

- result of granulocyte demargination
  - no absolute increase in WBC number

## Plasma derivatives

- **plasma derivatives** (such as factor VIII) are prepared from several thousand plasma donations, typically 20,000, or 5,000 kg of plasma at a time.
- **Pooled plasma** has been sourced from outside the UK since 1999 to avoid vCJD risks.
  - The process involves several chemical steps including:
    - ethanol extraction,
    - chromatography, and
    - **viral inactivation steps which results in a freeze-dried product.**
- **These products** have a long shelf life of several months to years.

## Cell saver devices

These collect patients own blood lost during surgery and then re-infuse it.

**There are two main types:**

- Those which wash the blood cells prior to re-infusion. These are more expensive to purchase and more complicated to operate. However, they reduce the risk of re-infusing contaminated blood back into the patient.
- Those which do not wash the blood prior to re-infusion.

Their main advantage is that they avoid the use of infusion of blood from donors into patients and this may reduce risk of blood borne infection.
It may be acceptable to Jehovah's witnesses.
It is contraindicated in malignant disease for risk of facilitating disease dissemination.

## Blood products used in warfarin reversal

Immediate or urgent surgery in patients taking warfarin:

- Stop warfarin
- Vitamin K (reversal within 4-24 hours)
  - IV takes 4-6h to work (at least 5mg)
  - Oral can take 24 hours to be clinically effective
- Fresh frozen plasma
  - Used less commonly now as 1st line warfarin reversal
  - $30ml/kg^{-1}$
  - Need to give at least 1L fluid in 70kg person (therefore not appropriate in fluid overload)
  - Need blood group
  - Only use if human prothrombin complex is not available
- Human Prothrombin Complex (reversal within 1 hour)
  - Bereplex 50 u/kg
  - Rapid action but factor 6 short half life, therefore give with vitamin K

## Neonatal exchange transfusion

- **An exchange transfusion requires blood which is plasma reduced whole blood in CPD (citrate phosphate dextrose/anticoagulant), irradiated and less than five days old.**
- The Rh group should either be Rh negative or identical to the neonate, to avoid haemolytic transfusion reaction in the neonate.

# Blood product transfusion complications

## Complications:

- **Hemolytic:** immediate or delayed
- **Non-hemolytic febrile** reactions
- Transmission of viruses, bacteria, parasites, **vCJD**
- Hyperkaliemia
- Iron overload
- ARDS
- Clotting abnormalities

## Immediate hemolytic reaction:

- e.g. ABO mismatch
- Massive intravascular haemolysis

## Febrile reactions:

- Due to white blood cell HLA antibodies
- Often the result of sensitization by previous pregnancies or transfusions
- It has a benign course.
- It is important to differentiate it from the haemolytic reaction
- **Treatment:**: stop transfusion + Paracetamol

## Causes a degree of immunosuppression

- e.g., patients with colorectal cancer who have blood transfusions have a worse outcome than those who do not

The common viral infections considered in the infective risks of a blood transfusion are hepatitis B, hepatitis C and HIV.

The risks are variable depending on the source of donation and the type of testing employed.

**In the United Kingdom:**

-The risks for **hepatitis B** are in the order of **1 per 1.3 million** donations while

- For **HIV** are **1 in 6.5 million** donations

- **Hepatitis C** and **1 in 28 million** donations.

A broad knowledge of the risks may be required while consenting a patient for blood transfusion.

**N.B:** Which type of infection is most likely to occur following a **platelet transfusion? >> Bacterial contamination.**

As platelet concentrates are generally stored at room temperature 22 °C, they provide a more favorable environment for bacterial contamination than other blood products.

In contrast packed red cells are stored at an average of 4°C while fresh frozen plasma as well as cryoprecipitate are stored at −30°C.

Factor VIII concentrates are heat inactivated freeze dried products with a minimal risk of bacterial contamination.

## Delayed hemolytic transfusion reaction:

It occurs **24 hours after** the transfusion.

Also it can be occur up to **5-10 days after** transfusion.

It is due to the development of red cells

This happens in a patient who **has been previously immunised** by transfusions or pregnancy.

The antibodies are not detectable initially but become obvious as a secondary immune response to the antigen exposure during the transfusion occurs.

Clinical features are usually **minimal** but can include **unexplained drop of Hb, unexplained pyrexia, jaundice** and **dark urine** after few days of transfusion.

**The following should be carried out:**

- Hb level
- Blood film: fragile ballooned spherocytes.
- LDH
- Serum bilirubin
- Haptoglobin
- **Direct Coombs test = Direct anti-globulin test (DAT):**
  - It detects the presence of antibody on RBCs.
  - The test is performed by adding AHG (Antihuman globulin) (anti-IgG and anticomplement) to the patient's washed RBCs.
  - A positive test results in RBCs agglutination.
- Renal profile
- Urinalysis for hemoglobinuria.

The group and antibody screen should be repeated.

**EX**: A patient on a medical ward received a transfusion **48 hours** ago for symptomatic anemia on a background of CKD and COPD.
He gives a history of previous transfusions in the last year.
The patient has now dropped his Hb by 20 g/L compared to his pre-transfusion level and reports a dark coloured urine.
The LDH and bilirubin are elevated.
The most likely to this is >>> **Delayed haemolytic transfusion reaction**:
DD: Transfusion-associated graft versus host disease (GVHD), and
DD: Acute hepatitis as an infective complication_both would be expected to occur in a one or two weeks.
DD: Acute hemolysis which would be expected to occur during the transfusion.

**EX**: A 75-year-old woman receives 2 units of packed red cells following a hip replacement. **One week later** her Hb concentration had fallen by 4 g/L.
The most likely to indicate a **delayed immune haemolytic transfusion reaction** is >>> **Positive direct anti-globulin test (DAT) being diagnostic.**

**EX**: Patient follow up **post-operative by 5 days** which he has received 2 units Packed RBCS, now he has drop of Hb 7, jaundice, dark urine >>>? **Delayed transfusion reaction** >>> Diagnosis by: **Direct Coombs' test**

**Transfusion related acute lung injury (TRALI)** occurs in patients **who have received** a multi-unit blood transfusion **previously** and are then re-transfused some time later e.g. in multiparous, she can develop **ARDS/ non cardiogenic pulmonary oedema** within 6 hours of blood transfusion.

Non cardiogenic pulmonary oedema can be differentiated from fluid overload by measurement of BNP.

It is diagnosed clinically and is thought to be significantly underdiagnosed.

It is thought to be related to **anti-HLA** or **anti-granulocyte antibodies** in the **donor** blood.

Despite the fact that the donor and recipient are matched, the possibility of anti-granulocyte antibodies cannot be excluded.

## Two hypotheses are proposed for the cause of TRALI that it is either

- Due to **HLA antigens in the donor blood** reacting with neutrophil antigens in the patient, leading to neutrophil migration to pulmonary capillaries

## Or that

- The neutrophils responsible do not actually require donor HLA antigens to react, and are just primed by infection, surgery or inflammation.

What is common to both hypotheses though, is that the neutrophils lead to a local release of cytokines, increased capillary permeability, and **non-cardiogenic pulmonary oedema**, accounting for the presentation with wheeze and hypoxia.

Diagnosis can be confirmed by the finding of **anti-HLA** or **antineutrophil antibodies** in the **donor** or **recipient**.

Mortality is at between 5-15% depending on case series.

## Treatment:

- Mainly by **full respiratory support** as the condition is reversible after few days, with possible transfer to **ICU** for consideration of intubation & Ventilation if required.
- **Donors** who carry such antibodies are **resigned** from the donor pool.
- When **recipients** who have developed TRALI require further transfusion, **male donor** can be used to reduce the risk of subsequent attacks, this is because they have a much lower rate of carriage of anti-HLA or antineutrophil antibodies (1-5% vs up to 20% in women).

**Blood products: FFP, cryoprecipitate and prothrombin complex**
NICE published guidelines on the use of blood products in 2015.

## Fresh frozen plasma (FFP)

- most suited for 'clinically significant' but without 'major haemorrhage' in patients with a prothrombin time (PT) ratio or activated partial thromboplastin time (APTT) ratio > 1.5
- typically, 150-220 mL
- can be used prophylactically in patients undergoing invasive surgery where there is a risk of significant bleeding
- In contrast to red cells, the universal donor of FFP is AB blood because it lacks any anti-A or anti-B antibodies

## Cryoprecipitate

- contains concentrated Factor VIII:C, von Willebrand factor, fibrinogen, Factor XIII and fibronectin, produced by further processing of Fresh Frozen Plasma (FFP). Clinically it is most commonly used to replace fibrinogen
- much smaller volume than FFP, typically 15-20mL
- most suited for patients for 'clinically significant' but without 'major hemorrhage' who have a fibrinogen concentration < 1.5 g/L
- example use cases include disseminated intravascular coagulation, liver failure and hypofibrinogenemia secondary to massive transfusion. It may also be used in an emergency situation for hemophiliacs (when specific factors not available) and in von Willebrand disease
- can be used prophylactically in patients undergoing invasive surgery where there is a risk of significant bleeding where the fibrinogen concentration < 1.0 g/L

## Prothrombin complex concentrate

- used for the emergency reversal of anticoagulation in patients with either severe bleeding or a head injury with suspected intracerebral hemorrhage
- can be used prophylactically in patients undergoing emergency surgery depending on the particular circumstance

## The most common indications for irradiated blood products include:

Those at risk of transfusion associated with graft versus host disease (GVHD) (it prevent viable T lymphocytes in the donation engrafting and causing transfusion-associated GVHD). Such cases as:

- Neonates
- Hodgkin's lymphoma.
- Those receiving purine analogues based chemotherapy.
- Immunodeficiency states.
- Post bone marrow transplantation.

## CMV negative and irradiated blood

Cytomegalovirus (CMV) is transmitted in leucocytes. As most blood products (except granulocyte transfusions) are now leucocyte depleted. CMV negative products are rarely required.

Irradiated blood products are depleted of T-lymphocytes and used to avoid transfusion-associated graft versus host disease (TA-GVHD) caused by engraftment of viable donor T lymphocytes.

CMV is a transfusion-transmitted infection that can be fatal in stem cell transplant recipients, so it is good practice to use CMV negative products

**Gamma Irradiation** of blood does not affect its quality.

Patients should be informed that they need irradiated blood products and given an information card.

The table below shows the indications for CMV and irradiated blood:

| Situation | CMV negative | Irradiated |
|---|---|---|
| Granulocyte transfusions | ✓ | ✓ |
| Intra-uterine transfusions | ✓ | ✓ |
| Neonates up to 28 days post expected date of delivery | ✓ | ✓ |
| Pregnancy: Elective transfusions during pregnancy (not during labour or delivery) | ✓ | |
| Bone marrow / stem cell transplants | | ✓ |
| Immunocompromised (e.g. chemotherapy or congenital) | | ✓ |
| Patients with/previous Hodgkin lymphoma | | ✓ |
| HIV | | |

The table below summaries some of the key features:

| Reaction | Features | Management |
|---|---|---|
| **Non-haemolytic febrile reaction**<br>Thought to be caused by antibodies reacting with white cell fragments in the blood product and cytokines that have leaked from the blood cell during storage | Fever, chills<br>Red cell transfusion (1-2%)<br>Platelet transfusion (10-30%) | Slow or stop the transfusion<br>Paracetamol<br>Monitor |
| **Minor allergic reaction**<br>Thought to be caused by foreign plasma proteins | Pruritus, urticaria | **Temporarily stop the transfusion**<br>**Antihistamine**<br>Monitor |
| **Anaphylaxis**<br>Can be caused by patients with IgA deficiency who have anti-IgA antibodies | Hypotension, dyspnoea, wheezing, angioedema. | Stop the transfusion<br>IM adrenaline<br>ABC support<br>oxygen<br>fluids |
| **Acute haemolytic reaction**<br>ABO-incompatible blood e.g. secondary to human error | Fever, abdominal pain, hypotension | Stop transfusion<br>Confirm diagnosis<br>check the identity of patient/name on blood product<br>send blood for direct Coombs test, repeat typing and cross-matching<br>Supportive care<br>fluid resuscitation |
| **Transfusion-associated circulatory overload (TACO)**<br>Excessive rate of transfusion, pre-existing heart failure | Pulmonary oedema, hypertension | Slow or stop transfusion<br>Consider intravenous loop diuretic (e.g. furosemide) and oxygen |
| **Transfusion-related acute lung injury (TRALI)**<br>Non-cardiogenic pulmonary oedema thought to be secondary to increased vascular permeability caused by host neutrophils that become activated by substances in donated blood | Hypoxia, pulmonary infiltrates on chest x-ray,<br>fever, hypotension | Stop the transfusion<br>Oxygen and supportive care |

**Post bone marrow transplant** with anaemia and in need PRBCs blood transfusion or with sever thrombocytopenia and in need for platelet transfusion >>> **Gamma Irradiated** & **CMV-negative** red cells or PLT.

**Post bone marrow transplant acute graft versus host disease (GVHD):**

This presents **within 100 days** of bone marrow transplantation.

But, chronic GVHD occurring 100-300 days post-transplant.

Presented with a **triad** of **skin rash** (can progress to Erythroderma), **liver dysfunction** (cholestatic jaundice) and **Diarrhea** (sometimes bloody).

GVHD is graded according to the Seattle system, and each organ involved is scored (**skin**, **liver** and **gut**).

It remains a **serious** cause of mortality and morbidity amongst BM TX Rx.

**Treatment: Pulse methylprednisolone IVI** + TPN ± tPA and prostacyclin only if associated with veno-occlusive disease.

Also add immunosuppresses as **cyclosporine**, Tacrolimus and MMF.

**EX:** A 33-year-old male develops a rash and low grade fever (37.6°C) 20 days post allogeneic bone marrow transplant for high risk AML in first complete remission. The rash is initially maculopapular affecting palms and soles but 24 hours later general Erythroderma is noted affecting the trunk and limbs. His total bilirubin was previously normal but is now noted to be 40 µmol/L (1-22). He remains very well in himself >>> **Acute GVHD** >>> **Treatment Pulse methylprednisolone IVI.**

**The storage conditions and shelf life of blood products:**

- **Red cells** are stored at **4°C** for up to **35 days** and
- **Platelets** at **22°C** for **5 days** on **a platelet shaker/agitator.**
- **Fresh frozen plasma** can be stored **up to 24 months** at **−30°C.**

The **minimum dataset** for identifying a patient and a sample for purpose of a non-emergency blood transfusion: **Full name**, **DOB** and **patient ID**.

Address (in some areas, such as Wales),

Previous blood grouping details are not required

The **most common error** in transfusion according to the **SHOT** (serious hazards of transfusion) analysis is >>> **Wrong identification or mislabelling of patient or sample or requests.**

Other errors such as cross match error, incorrect storage and transfusion reaction due to an antibody not detected do occur but are rare.

**A 'group and save'** is adequate for **elective** surgeries and is standard practice in most modern blood banks. This will involve blood grouping and its confirmation as well as an antibody screen.

Other options include cross match and a direct Coombs' test (Direct anti-globulin test or DAT) which are often done only if the antibody screen test is positive. These are not routinely done for elective surgery unless the patient has had a recent blood transfusion or a history of previous known red cell antibodies.

In a stable patient **red cell packs (PRBCs)** may be transfused **over 90-120 minutes** while a **platelet** transfusion should **not take more than 20-30 minutes.**

Rapid infusion of PRBCs or FFP may be required in acutely bleeding patient but not in this patient who is stable.

**Manufacture of pooled plasma derivatives:**

- The plasma derivatives (such as factor VIII) are prepared **from several thousand plasma donations**, typically 20,000, or 5,000 kg of plasma at a time.

- **Pooled plasma** has been sourced from **outside UK** since **1999** to avoid **vCJD** risks.

- The process **involves several chemical steps** including ethanol extraction, chromatography and **viral inactivation steps** which results in **a freeze dried product.**

- These products have a **long shelf life** of **several months to years.**

The **blood** to be used for an **exchange transfusion** in a **neonate** should fulfil the following criteria: **plasma reduced whole blood** in CPD (citrate phosphate dextrose/anticoagulant), **irradiated** and **less than 5-days-old.**

The **Rh** group should be **compatible with the mother, not the neonate**, to avoid haemolytic transfusion reaction in the neonate due to maternal Rh antibodies.

**EX**: A 45-year-old woman being treated for acute myeloid leukaemia (AML) fails to get sufficient rises with platelet transfusions. She is 14 days post chemotherapy, afebrile and apart from minor bruising is otherwise well.

The next best step in the management of **platelet refractoriness >>> Check for a one hour post platelet transfusion platelet count.**

Patients who are **refractory to platelet transfusions** should **first** be investigated to **check for adequate platelet rises**. This is best done **on a one or two hour post platelet transfusion sample.**

Further management would include checking for **HLA antibodies** but requesting HLA matched platelets at this stage would not be appropriate.

Continuing random platelet transfusions or requesting a directed platelet donation are also not appropriate at this stage.

Platelets are obviously indicated in this patient until recovery of blood counts and hence cannot be avoided.

- **Blood Group O**: The red cells have absent A/B antigen and plasma has anti A and anti B antibodies.
- **Blood Group AB**: The red cells have A /B antigen but no antibodies in the plasma.
- **Blood Group A**: The red cells have antigen A and plasma has anti B antibodies.
- **Blood Group B**: The red cells have antigen B and plasma has A antibodies.

Approximately **1% of pregnant women** develop clinically important red cell antibodies, the most common being **rhesus antibodies**.

The women negative for D antigen develop antibodies on exposure to D positive blood (such as fetomaternal haemorrhage (FMH), abortions and transfusions).

This increases the risk of haemolytic disease of the Newborns (**HDN**) in **subsequent** pregnancies.

**Following delivery**, the **degree of fetomaternal haemorrhage (FMH) should be calculated on a blood sample from a D negative mother** to adjust the dose of anti D in the D negative mother delivering a D positive child.

D positive women and D negative women have the **same chances** of developing antibodies to other red cell antigens.

All pregnant women should have a **blood group and antibody screen** in their **first** trimester or at presentation, whichever is earlier.

The fetal Rh type depends on the paternal and maternal Rh typing.

Maternal antibody **titres correlate** with the degree of haemolytic disease of the newborn (HDN).

If a **female patient** has been given **Rh D positive platelets** when she is **RhD negative**, she is therefore by now (five days later) likely to have made **immune anti-D**.

It is very often necessary to give D positive platelets to D negative people due to platelet shortage.

If the recipient of this mismatch is a **female of child bearing age** then **prophylactic anti- D should be administered with the platelets** to prevent production of immune anti- D.

If she become pregnant in the future, the immune anti-D she has made can cross the placenta and **cause haemolytic disease of the fetus/newborn,** if the **baby is D positive**, and this can be life threatening to the baby.

Therefore any pregnancies would have to be managed by an obstetrician with special interest in fetal medicine and the baby closely monitored and the **levels of anti-D in the mother** monitored.

## Plasma exchange

### Indications for plasma exchange (also known as plasmapheresis)

- Guillain-Barre syndrome
- myasthenia gravis
- Goodpasture's syndrome
- ANCA positive vasculitis e.g. Wegener's, Churg-Strauss
- TTP/HUS
- cryoglobulinaemia
- hyperviscosity syndrome e.g. secondary to myeloma

## Hyposplenism

### Causes:

- Splenectomy
- Sickle-cell
- SLE
- Coeliac disease, dermatitis herpetiformis (HLA DR3).
- Graves' disease
- Amyloid

### Features:

- **Howell-Jolly bodies**
- **Siderocytes**

## Blood films: more details

**Hyposplenism e.g., post-splenectomy SLE and coeliac disease** (occurs in around 30% of coeliac patients)

- **Target cells**
- **Howell-Jolly bodies** (DNA remnanat)
- **Pappenheimer bodies** (Siderotic granules)
- Acanthocytes

**Iron-deficiency anemia**

- **Target cells**
- **'Pencil' poikilocytoses**
- If combined with B12/folate deficiency a **'dimorphic' film** occurs with mixed microcytic and macrocytic cells

**Megaloblastic anemia:** Hypersegmented neutrophils

**Myelofibrosis: 'Tear-drop' poikilocytes**

**Intravascular hemolysis:** Schistocytes

**EX:** Blood film with **Howell-Jolly bodies and pencil cells** (i.e. hyposplenism + IDA) both are seen in **Coeliac disease**

### Stains & reagents used in Hematology

| | |
|---|---|
| Tartrate Resistant Acid Phosphatase (TRAP) | Hairy cell leukaemia |
| Sudan black B stain and myeloperoxidase | AML |
| Terminal Deoxynucleotide Transferase Stain (TDT) | ALL |
| Leukocyte Alkaline Phosphatase (LAP) | ↑ in Leukemoid reaction, PRV and Myelofibrosis.<br>↓ in CML. |

### Congenital Pelger–Huet anomaly

- is a laminopathy associated with mutations in the lamin B receptor.
- This leads to **bilobed nuclei in neutrophils** and in homozygotes,
- can also be associated with:
  - skeletal abnormalities which include shortened limbs.
  - Like this patient, heterozygotes usually suffer no symptoms and the neutrophil anomaly is picked up as an incidental finding.

**MRCP part 1 exam:** A 23-year-old man with tiredness and was noted to have a **neutrophil abnormality** on his blood film with **bilobed nuclei.** His father has a skeletal anomaly with a short right arm, Examination reveals no lymphadenopathy, and abdominal examination is entirely normal. What is the most likely diagnosis? **>> Congenital Pelger–Huet anomaly**

## Iron deficiency anemia (IDA)

**Anemia is present in adults** if the hematocrit is below 41% (hemoglobin less than 13.6gm/dl in males or below 12 gm/dl in females. Most common type is iron deficiency anemia

**Causes:** the commonest cause of iron-deficiency anaemia worldwide being hookworm infection (**Necator americanus** and *Ancylostoma duodenale*), which affects 25% of the global population.

**Features:**

In addition to pallor, easy fatiguability, palpitation which are common feature of any type of anemia, the specific features are:

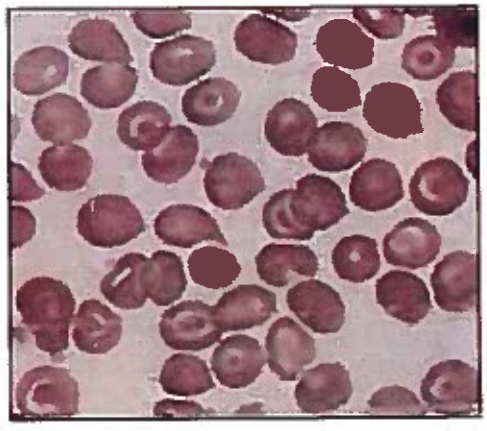
- Angular stomatitis.
- Atrophic glossitis.
- Post-cricoid webs.
- Koilonychia.

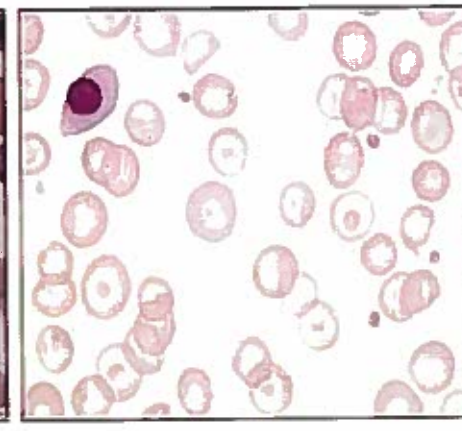
## Investigations

### Blood film:

- **Target cells**
- **'Pencil' poikilocytes**
- **If combined with B12/folate deficiency a 'dimorphic' film** occurs with mixed microcytic and macrocytic cells.

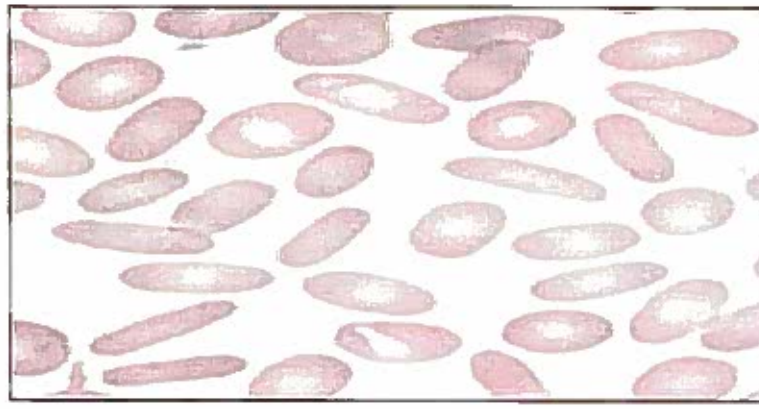
**Blood film:Note the hypochromic and microcytic features, that the area of central pallor is enlarged and that there is an occasional target cell and pencil cell.**





### Target cells Seen in:

- Hyposplenism
- Iron-deficiency anemia
- Sickle-cell/thalassemia
- Liver disease



**'Pencil' poikilocytes: in Iron deficiency anemia**

## Tips

A. **Low SERUM FERRETIN level (less than 12ng/ml or less than 30 ng/ml if also anemic and low TRANSFERRIN SATURATION** are consistent features of iron deficiency anemia.

B. **Reticulocytosis occurs in one of three pathophysiology:**
- Acute blood loss.
- Recent replacement of erythropoietic elements.
- Reduced red blood cells survival (i.e.haemolysis)

C. **A microcytic anemia in a female** should raise the possibility of either gastrointestinal blood loss or menorrhagia, if accidentally discovered during pregnancy with extremely low MCV think of thalassemia trait.

D. Absorption of oral iron is improved by **vitamin C ascorbic acid.**

E. Ferrous **sulphate** has more elemental iron by mass than the same dose of ferrous gluconate

F. Iron is absorbed in the **upper small intestine.**

G. **Parenteral** iron acts **no faster than oral iron.** It is indicated when **oral iron** cannot be **tolerated** or is **not absorbed** or patient received oral iron for three months without response.

H. **Sustained release** preparations may improve **tolerance** of oral iron but do not aid absorption.

I. **Zinc deficiency** is important cause of poor iron absorption.

## Iron metabolism

### Absorption:

- **Upper small intestine.**
- About 10% of dietary iron absorbed.
- **Fe2+ (ferrous** iron) much better absorbed than Fe3+ (ferric iron).
- Absorption is regulated according to body's need.
- **Increased by vitamin C and gastric acid.**

- **Decreased** by PPIs, tetracycline, gastric achlorhydria, tannin (in tea).
- From an intake of approximately 6 mg/1000 kcal of dietary iron **only 15% is bioavailable.**

**Distribution in body:**

- **Total body iron** = **4g** (2500 mg in the RBCs, 500 mg in liver, 500 mg in macrophages and about 500 mg in muscle). Approximately **4 mg** of iron circulate within the plasma. **So approximately 0.1% of body iron circulates in the plasma.**
- **Hemoglobin = 70%**
- Ferritin and hemosiderin = 25%
- Myoglobin = 4%
- Plasma iron = 0.1%

The majority of iron found in the body is in **Haemoglobin** about **70%.**

**Transport:** Carried in **plasma** as **Fe3+** bound to **transferrin.**

**Storage:** Stored as **ferritin** in **tissues.** It is the plasma protein responsible for binding iron, is an acute phase reactant protein which is **increased** in inflammatory conditions following surgery.

**Excretion:** Lost via intestinal tract following desquamation. The majority of iron contained within the RBCs is metabolised and re-utilised but 1 mg per day is lost through the gut.

**Transferrin** is a glycoprotein responsible for internal iron exchange and the content within **mucosal cells** is naturally **high** in **haemochromatosis** with **high iron store saturation**.

$Fe^{2+}$ (ferrous iron) is oxidised to $Fe^{3+}$ (ferric iron) by caeruloplasmin to bind to **transferrin** which is about **one third saturated** with **iron**.

In absence of anaemia, **transferrin** is about **33% saturated** with **iron**.

**Iron (Fe 3+)** is carried in the blood bound to transferrin.

**Pregnancy and the oral contraceptive pill (OCP) both increase transferrin.**

The **transferrin saturation %** (plasma iron /TIBC x 100) is used as a measure of iron **stores**. A value **below 16%** is indicative of **iron deficiency**.

In **iron deficiency** >>> **low** serum Fe, **rise** TIBC, **rise** the transferrin level.

In **iron overload** >>> **fall** in both TIBC and transferrin.

In **haemochromatosis** >>> **increased** in **Transferrin saturation%.**

**Refractory iron deficiency to oral iron is defined as:** Hemoglobin increment of less than 1gm/dl after 4-6 weeks of 100mg /day of elemental oral iron:

- autoimmune gastritis.
- H. pylori gastric infection.
- celiac disease.
- hereditary iron deficiency anemia.

## Oral iron therapy:

**Ferrous sulfate 325 mg once daily or every other day.**

**An appropriate response is a return of the hematocrit level half way toward normal within 3 weeks. with full return to baseline after two months. iron therapy should continue for 3-6 months. after restoration of normal hematological values to replenish iron stores.**

## Indications for IV iron include:

- Patients requiring iron supplementation who are **unable to tolerate** compounds given orally, or
- Patients who **fail to comply** with prescriptions for oral iron supplementation.
- Patients with **gastro-intestinal disorders**, such as inflammatory bowel disease (ulcerative colitis and Crohn's disease), in which symptoms may be aggravated by oral iron therapy, or
- Patients who are unable to maintain acceptable iron levels during treatment with **haemodialysis.**

It is considered best practice to administer **1000 mg** of **low** molecular weight iron dextran in **250 mL of normal saline in 1 hour without premedication**; a **test dose of 10 to 25 mg is infused over 3 to 5 minutes** prior to the first infusion.

If no acute reaction is observed, the remaining solution is infused over the balance of 1 hour.

For **those** with a history of drug allergies or hypersensitivity, **125 mg of methylprednisolone is infused prior to the test dose.**

## Iron studies

- **Serum iron**
- **Total iron binding capacity (TIBC)**
- **Transferrin**
  - raised in iron deficiency anemia (IDA)
  - raised in pregnancy and by estrogen
- **Transferrin saturation:** calculated by serum iron / TIBC
- **Ferritin**
  - raised in inflammatory disorders
  - low in IDA
- **Rarer tests:** transferrin receptors >> increased in IDA
- **Anemia of chronic disease**
  - normochromic/hypochromic, normocytic anemia
  - reduced serum and TIBC
  - normal or raised ferritin

## Methaemoglobinaemia

It describes Hb which has been **oxidized from Fe++ (ferrous) to Fe+++ (Ferric). (Fe++ >> Oxidation >> Fe+++)**
This is **normally** regulated by **NADH methemoglobin reductase**, which transfers electrons from NADH to methemoglobin resulting in the reduction of methemoglobin to hemoglobin.
There is **tissue hypoxia** as Fe+++ cannot bind oxygen, and hence the oxygen-Hb dissociation (oxidation-dissociation) curve is **shift to left.**

### Congenital causes:

- Hb chain variants: HbM, HbH
- **NADH methaemoglobin reductase deficiency.**

### Acquired cause:

**Drugs:**

- **Na Nitroprusside,**
- **Nitrates,**
- **Drinking water contaminated with nitrates,**
- Drinking a **flask of amyl nitrate (in nightclub),**
- **Primaquine (malaria prophylaxis ttt),**
- **Sulphonamides (Trimethoprim),**
- **Dapsone.**

**Chemicals: Aniline dye.**

## Features:

- **Chocolate central cyanosis,** the blood also appears chocolate brown when compared with normal blood.
- **Dyspnea.**
- **↓ Oxygen saturation** with **NORMAL PO2**
- Despite increase oxygen delivery even the non-rebreather mask, the O2 saturation remain low.
- Severe: **acidosis**, **anxiety**, arrhythmia, seizures, coma.

**Severity** of symptoms usually correlates with **measured methemoglobin (Met Hb) levels:**

- Mild methemoglobinemia (< 15-20%) usually resolve spontaneously and requires no intervention.
- The discolouration of blood and appearance of cyanosis manifests when the MetHb levels reach **15-20%.**
- Levels between 20-45% are associated with dyspnoea, lethargy, dizziness and headaches.
- MetHb levels above 45% are usually associated with impaired consciousness
- Levels above 55% can cause seizures, coma and cardiac arrhythmias.
- The lethal concentration for adults is considered to be more than 70%.

## Management:

- **Methylene blue 1% IVI (1-2 mg/kg IVI over several minutes):** in acquired causes. It is the **initial** treatment of choice especially when methaemoglobin level is >20%, it should be administered with care as at high dose > 7 mg/kg it becomes an oxidant itself.
- **Ascorbic acid**: in NADH methaemoglobin reductase deficiency. It is a second line therapy although some debate exists as to its efficacy.
- **Exchange transfusion.**
- **Hyperbaric** oxygen therapy

**EX:** Pt take Dapsone for malaria prophylaxis before trip to Kenya, the presented with confusion, tachypnea, desaturation, tachycardia, hypotension, anaemia HB 8, ↑RTX >>>> the diagnosis is that of **methaemoglobinaemia secondary** to **Dapsone** in a patient with underlying (**G6PD**) deficiency >>> **Treatment: Exchange blood transfusion.**

Methaemoglobinaemia in G6PD-deficient patients is best treated with **exchange transfusion.**

**NB:** Methylene blue is contraindicated in patients with G6PD deficiency as it can lead to severe haemolysis.

# Thalassemia

It is a haemoglobinopathy resulting from defective synthesis of globin chains required for Hb synthesis.

Each copy of **chromosome 16** has two genes for the **alpha globin** subunit (**four** in total).

And each copy of **chromosome 11** has one gene for the **beta globin** subunit (**two** in total).

- Adult Hb= **HbA (α2β2)** (Normal > **95%**)
- Second adult Hb= **HbA2 (α282)** (Normal < **3.5%**),
- Fetal Hb=**HbF (α2γ2)** (Normal < **1.5%**)

## Alpha-thalassemia:

Alpha-thalassemia is due to a deficiency of alpha chains in hemoglobin.
**2 separate alpha-globulin genes** are located on each **chromosome 16.**
Clinical severity depends on the number of alpha chains present:

- **If 1 (aa/-a) or 2 (aa/--) alpha chains are absent** then the blood picture would be hypochromic and **microcytic, but the Hb level would be typically normal.**
- Loss of 3 alpha chains results in a hypochromic microcytic anaemia with splenomegaly. This is known as **Hb H** disease, thalassemia intermedia.
- If all 4 alpha chains absent (--/--) (i.e., homozygote) then death in utero (hydrops fetalis, Bart's hydrops, gamma 4 tetramer).

**I.e., we ca say that in α-thalassemia:**

- **1 gene deletion** (aa/-a): **Silent carrier.**
- **2 gene deletion** (aa/--): **α-thalassaemia trait** (↓ HbA2).
- **3 gene deletion** (a-/--): **HbH** (β4): moderate anaemia, splenomegaly.
- **4 gene deletion** (--/--): **Hydrops fetalis, Bart's Hb** (γ4).

## Beta-thalassaemia:

Beta-thalassaemias are due to mutations in the HbB gene on **chromosome 11,** also inherited in an **autosomal recessive** fashion.

The severity of the disease depends on the nature of the mutation.

**Mutations are characterized as:**

- **$\beta^0$** or β thalassaemia major: if they prevent any formation of β chains, which is the most severe form of β thalassemia.
- **$\beta^+$** or **β thalassaemia intermedia**: if they allow some β chain formation to occur.

In either case there is relative excess of α chains, but these don't form tetramers. Rather they bind to the RBC membranes producing membrane damage and at high concentrations they form toxic aggregates.

- **1 gene deletion: β thalassaemia minor / trait:** (**mild** microcytic hypochromic anemia, **marked microcytosis (very low MCV)**, **↑HbA2 > 3.5%,** it is usually **asymptomatic**. Microcytosis is characteristically **disproportionate** to the anemia. (i.e. the Microcytosis is disproportionately with very low MCV for the near normal Hb level >9).
- **2 gene depletion ($\beta^0$ / $\beta^0$): β thalassaemia major: anemia** when HbF tries to convert to HbA during **first year of life,** extramedullary hemopoiesis with **hepatosplenomegaly** and bone marrow expansion, "hair on end" appearance of bone.

The terms thalassemia minor, intermedia & major do not pertain to α- or β-thalassemia rather they describe whether the patient is asymptomatic (minor), transfusion dependent (major) or in between (intermedia).

**Ex:** 23-year-old **Chinese** woman presents with lethargy, **Hb 10.5%, MCV 60** fl, Blood film: Microcytic hypochromic RBCs, marked anisocytosis and basophilic stippling noted, **HbA2 = 4%.**

What is the most likely diagnosis? >> **Beta-thalassemia trait.**

Microcytic anemia would immediately raise the suspicion of iron deficiency perhaps from GIT or menstrual blood loss. However, the **MCV here is disproportionately low**. This combined with a **raised HbA2** makes the diagnosis of **beta-thalassemia trait** the most likely diagnosis.

**Note that in cases of severe iron deficiency anemia the HbA2 may be normal in thalassemia minor.**

**EX:** Pt 44 years old, Hb 9, MCV 60, FOB +ve, HbA2 is normal >>> **Co-existing B-Thalassemia minor and iron deficiency anemia**, and need to rule out GIT blood loss.
**Beta thalassemia major** is characterized by **anemia, splenomegaly, bone deformities** and **early death if** not treated appropriately.
A **transfusion program with iron chelation is the best initial approach.**
The transfusion related iron overload, which can be managed with iron chelation, both IV/SC (desferoxamine) and/or oral (deferasirox).
The next of kin should be offered screening >> the parents and other siblings should be **screened by genetic testing.**
**Desferoxamine** binds iron but needs to be given for 8-12 hours a day for 5-7 days per week, so is a major undertaking for the patient. Side effects: high frequency deafness, retinopathy and Yersinia infection.

## Beta thalassaemias (reduction in beta globin chains)

| Type | Genotype | Typical findings on CBC | Haemoglobin analysis (HPLC or electrophoresis |
|---|---|---|---|
| **Major** (transfusion-dependent) | $\beta^0 / \beta^0$ **or** $\beta^0 / \beta^+$ | **Severe** microcytic anaemia with target cells (typical Hb 3 to 4 g/dL) | HbA2 (**5%** or more). HbF (up to 95%) **No HbA** |
| **Intermedia** (non- transfusion-dependent) | $\beta^+ / \beta^+$ | **Moderate** microcytic anaemia | HbA2 (**4%** or more). HbF (up to 50%) |
| **Minor** (also called trait or carrier) | $\beta / \beta^0$ **or** $\beta / \beta^+$ | **Mild** microcytic anaemia | HbA2 (**4%** or more). HbF (up to 5%) |

$\beta^0$ refers to no beta globin production.
$\beta^+$ refers lo decreased beta globin production.

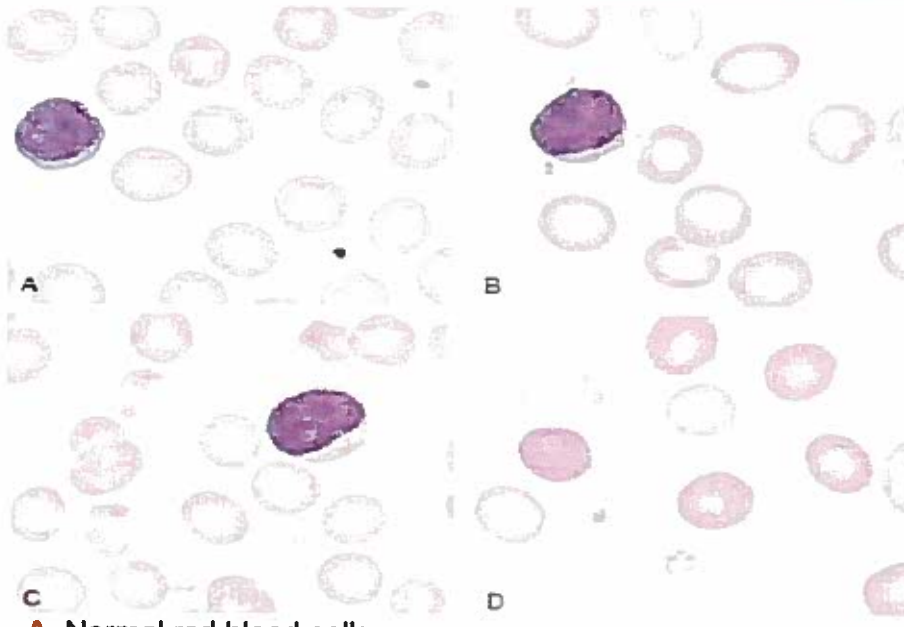
## Delta thalassemia:

As well as alpha and beta chains being present in Hb, about 3% of adult Hb is made of alpha and delta chains.

Just as with Beta-thalassemia, mutations can occur which affect the ability of this gene to produce delta chains.

Thalassemia can co-exist with other haemoglobinopathies. The most common of these are:

- **HbE/thalassaemia**: common in Cambodia, Thailand, and parts of India: clinically similar to β thalassaemia major or thalassaemia intermedia.
- **HbS/thalassaemia**: common in African and Mediterranean populations: clinically similar to sickle cell anaemia with additional feature of splenomegaly.
- **HbC/thalassaemia**: common in African and Mediterranean populations:
    - **HbC/β0 thalassaemia**: causes moderate to severe haemolytic anaemia with splenomegaly.
    - **HbC/β+ thalassaemia**: produce a milder disease.




- **A,** Normal red blood cells.
- **B,** Microcytosis and hypochromia (MCV. 70 fL) caused by iron deficiency.
- **C,** Microcytosis and hypochromia resulting from -thalassemia trait (MCV, 67 fL).
- **D,** Dimorphic red blood cells caused bv sideroblastic anemia

## Sideroblastic anaemia

- Sideroblastic anemia is a condition where red cells fail to completely form hem, whose biosynthesis takes place partly in the mitochondrion.
- This leads to **deposits of iron** in the **mitochondria** that form a ring around the nucleus called a **ring sideroblast.**
- It may be congenital or acquired:

**Congenital cause:** delta-aminolevulinate synthase-2 deficiency.

**Acquired causes:**

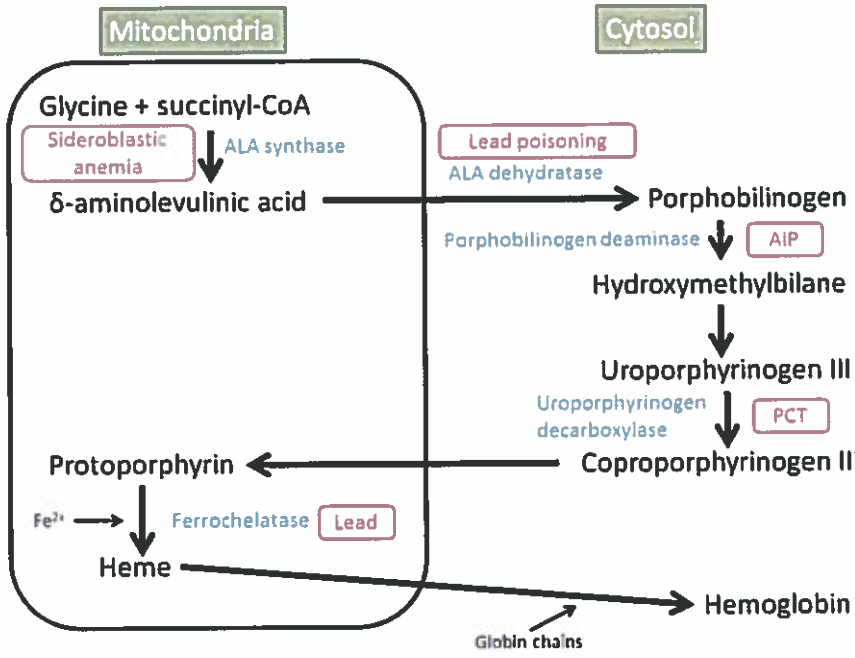
- **Lead**
- **Alcohol**
- **Myelodysplasia**
- **Drugs: Anti-TB medications, chloramphenicol.**

**Investigations:**

- **Hypochromic microcytic anemia** (more so in congenital)
- **Bone marrow**: sideroblasts and increased iron stores in Bone Marrow.

## Management:

- Supportive
- Treat any underlying cause
- **Pyridoxine** may help
- Treat any underlying cause




# Aplastic anaemia

- Characterized by pancytopenia and a hypoplastic bone marrow
- Peak incidence of acquired = 30 years old

## Features

- Assessment of bone marrow cellularity is best made on **trephine biopsy**, which often shows replacement of the normal cellular marrow by **fatty marrow.**
- normochromic, normocytic anaemia
- leukopenia, with lymphocytes relatively spared
- thrombocytopenia
- may be the presenting feature acute lymphoblastic or myeloid leukemia
- a minority of patients later develop paroxysmal nocturnal hemoglobinuria or myelodysplasia
- In patients with aplastic anemia, the bone marrow is markedly **hypocellular**.

## Causes

- idiopathic
- congenital: Fanconi anemia, dyskeratosis congenita
- drugs: cytotoxics, chloramphenicol, sulphonamides, phenytoin, gold
- toxins: **benzene**
- infections: parvovirus, hepatitis
- radiation

## Management

### Supportive

- blood products
- prevention and treatment of infection

**Anti-thymocyte globulin** (ATG) and anti-lymphocyte globulin (ALG)

- prepared in animals (e.g. rabbits or horses) by injecting human lymphocytes
- is highly allergenic and may cause serum sickness (fever, rash, arthralgia), therefore steroid cover usually given
- immunosuppression using agents such as ciclosporin may also be given

### Stem cell transplantation

- allogeneic transplants have a success rate of up to 80%

## Fanconi's Anemia:

- Autosomal recessive
- Aplastic anaemia
- ↑ risk of AML
- Neurological manifestation
- Skeletal abnormalities
- Skin pigmentation (café; au lait spots)

# Pure Red Cell Aplasia (PRCA)

## It is diagnosed when:

- Severe unexplained anemia
- ↓Reticulocyte count <1%
- The presence of less than 0.5% mature erythroblasts in the bone marrow
- Normocellular bone marrow in most cases

## It occurs either spontaneously or associated with:

- **Thymoma**
- Autoimmune
- Lymphoproliferative disorder

**Erythropoietin-induced pure red cell aplasia in treatment of CKD anaemia**

**Treatment:**

- Immunosuppressive: Cyclosporine.
- Erythropoietin **(but check firstly the Anti- Erythropoietin Abs).**

**EX:** Pt with **ESRD on dialysis** and **EPO**, she is tired and has **anaemia Hb 5** gm%, although on EPO >>>? **Pure red cell aplasia**, confirm by **bone marrow** >>> absent erythropoiesis, normal myeloid, plentiful megakaryocytes and no infiltrates >>> **Treatment: withdraw EPO** with subsequent falling of antibody levels.

## Paroxysmal nocturnal hemoglobinuria (PNH)

It is an acquired disorder leading to **haemolysis** (mainly **intravascular**) of hematological cells.

It is thought to be caused by increased sensitivity of cell membranes to complement due to a lack of **glycoprotein glycosyl-phosphatidylinositol** (GPI).

PNH is a disorder in which the cells **lack surface proteins** such as Delay Accelerating Factor **CD 55 (DAF)** and Membrane Inhibitor of Reactive Lysis **CD 59 (MIRL)**.

As a result, the RBCs are sensitive to destruction by complement and platelets are activated, these cause **intravascular haemolysis with dark morning urine** and **recurrent thrombotic events**.

Patients are at increased risk of **aplastic anaemia** and **leukopenia**.

Patients are more prone to **venous thrombosis (DVT/PE, Budd-Chiari Syndrome).**

Patients have **pancytopenia** and have a **pro-thrombotic** tendency with DVTs.

**Abdominal pain** is a common symptom and may be due to small mesenteric vein thrombi.

**Hemolysis** is **intermittent** - classically **nocturnal** - giving the **morning** urine a typical **dark** appearance.

## Pathophysiology: (Post-translational modification)

- GPI can be thought of as an anchor which attaches surface proteins to the cell membrane.
- Complement-regulating surface proteins, e.g. decay-accelerating factor (DAF), are not properly bound to the cell membrane due a lack of GPI.
- **Thrombosis is thought to be caused by a lack of CD59 on platelet membranes** predisposing to platelet aggregation.

## Features:

- **Hemolytic anemia**
- **Pancytopenia** may be present: Red blood cells, white blood cells, platelets or stem cells may be affected.
- **Aplastic anemia** may develop in some patients
- **Hemoglobinuria**: classically **dark-coloured urine** in the **morning,** (although has been shown to occur throughout the day), **urine is +ve for blood (haemoglobin) but no red cells.**
- **Thrombosis** e.g. **Budd-Chiari syndrome, DVT/PE.**

PNH = **Intravascular haemolysis + Thrombosis + Pancytopenia**

## Diagnosis:

- **Flow cytometry of blood to detect low levels of CD55 and CD59 has now replaced Ham's test as the gold standard investigation in PNH.**
- Positive Ham's test (sucrose lysis test): acid-induced haemolysis (normal red cells would not), it has low sensitivity.

The gold standard investigation in PNH >> **Flow cytometry** of blood to detect **low** levels of **CD55 and CD59.**

## Management:

- Blood product replacement
- **Anticoagulation**
- **Eculizumab**, a monoclonal antibody directed **against terminal protein C5**, and is showing promise in reducing intravascular hemolysis. But increase risk of meningococcal infection and those receiving it should receive the vaccine in advance.
- **Stem cell transplantation.**

**EX**: Male pt. 33 years old, has **breathlessness** for 3 months, **pallor, DVT** on warfarin for 6 months, dark urine. Lab: **Hb 6,** TLC 3, PLT 70, ↑ RTX and **urine + ve blood +++ >>> PNH.**
**EX**: Male Pt 33 years old with recurrent LL DVT, abdominal pain, jaundice and pancytopenia >>> **PNH.**

**EX:** Female 33 years old, severe fatigue, dark urine, severe abdominal pain, abdominal distension with ascites, **enlarged tender liver**, pallor, jaundice, Hb 8, TLC 3.3, PLT 90, ALT 200, bilirubin 55, urine hemosiderin and bilirubin +, US: enlarged liver, ascites, **absent flow in hepatic veins >>> PNH (Budd-Chiari syndrome).**

## Leukoerythroplastic Anemia

It is left shifted granulocytic series and nucleated RBCs with pancytopenia.

It is also defined when there are **immature cells** e.g. **myelocytes** and **nucleated RBCs** seen on the peripheral blood film.

### Association:

- ↑Bone marrow turnover e.g. in severe haemolytic anaemia (↑RTX).
- Myelofibrosis and CML (↑TLC, ↑PLT, Splenomegaly).
- Bone marrow invasion.
- Myeloma
- PRV
- Osteopetrosis
- T.B infiltration of bone marrow.
- Sarcoidosis

## Hemolytic anemias: by site (Intra/Extra Vascular)

**In intravascular haemolysis free Hb is released which binds to haptoglobin.**

As haptoglobin becomes saturated, Hb binds to albumin forming methemalbumin (detected by Schumm's test).

Free Hb is excreted in the urine as hemoglobinuria, hemosiderinuria.

| Intravascular haemolysis: causes | Extravascular haemolysis: causes (usually abnormal RBCs shape) |
|---|---|
| ➢ Mismatched blood transfusion.<br>➢ Red cell fragmentation: heart valves, HUS, TTP, and DIC.<br>➢ PNH<br>➢ **C**old AIHA<br>➢ **G**6PD deficiency* (also Extra) | ➢ **H**aemoglobinopathies: sickle cell, thalassemia.<br>➢ **H**ereditary spherocytosis<br>➢ **H**aemolytic disease of newborn.<br>➢ **W**arm AIHA. |

**N.B:** Strictly speaking there is an element of extravascular hemolysis in G6PD as well, although it is usually classified as an intravascular cause.

# Autoimmune hemolytic anemia (AIHA)

- It may be divided in to **'warm'** and **'cold'** types, according to at what temperature the antibodies best cause hemolysis.
- It is most commonly idiopathic but may be secondary to a lymphoproliferative disorder, infection or drugs.
- **AIHA is characterized by a positive direct antiglobulin test (AGT) (Direct Combs' test).**

## Warm AIHA:

- In warm AIHA the antibody (usually **IgG**) causes haemolysis best at body temperature and hemolysis tends to occur in **extravascular** sites, for example in the liver and spleen, so measurement of hemoglobinemia/ hemoglobinuria/ hemosiderin will be negative.
- **Management** options include steroids, immunosuppression and splenectomy.
- **Blood transfusion** can be life-saving until **immunosuppression** can take effect.
- The bone marrow responds by increasing RBCs production, which will be evident in peripheral blood by increase in the **reticulocytes**, immature RBCs, which will have **high MCV**.
- All patients with active hemolysis are at risk of acquiring folate deficiency due to increased metabolic demands and all should receive **folic acid** replacement therapy.
- **Management**
- treatment of any underlying disorder
- steroids (+/- rituximab) are generally used first-line

## Causes of warm AIHA:

- **Autoimmune disease:** e.g., **RA, SLE**
- Neoplasia: e.g., lymphoma, **CLL**
- Drugs:
  - e.g., **Penicillin**, **penicillin derivatives**, **Cephalosporins**, Methyldopa, levodopa, NSAIDs and Quinidine.
  - Treatment: stop the offending drug ± short course of oral prednisolone.

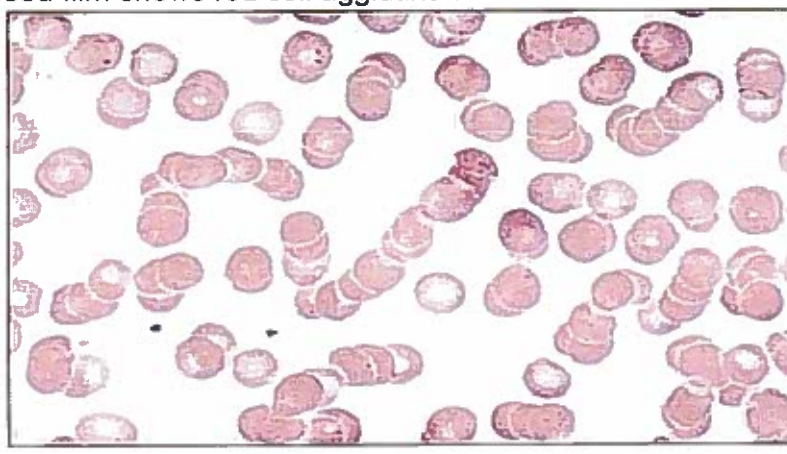
*SLE can rarely be associated with a mixed-type AIHA.

## Cold AIHA:

- The antibody in cold AIHA is usually **IgM** and causes hemolysis best at **4° C**. Hemolysis is mediated by complement and is more commonly **intravascular**.
- Features may include symptoms of **Raynaud's** and **acrocyanosis**.

- Patients respond less well to steroids.

Blood film shows red cell agglutination



➢ The blood film shows red cell agglutination, suggesting the presence of cold agglutinin which is associated with
  - Lymphoma {autoantibodies with anti-I specificity)
  - Mycoplasma pneumonia {autoantibodies with anti-I specificity)
  - Infectious mononucleosis {autoantibodies with anti-I specificity).
  - C3 is detected on the RBC surface by the direct antiglobulin test (DAT)

## Causes of cold AIHA:

- **Primary**: idiopathic cold haemagglutinin disease
- **Secondary** to:
  - Neoplasia: e.g., lymphoma
  - **Infections**: e.g., Mycoplasma pneumonia, EBV

| | Warm AIHA | Cold AIHA |
|---|---|---|
| **Definition** | haemolysis best at body temperature | haemolysis best at 4 deg C |
| **antibody** | **IgG** | **IgM** |
| **Site of haemolysis** | **extravascular** (e.g: spleen) | **intravascular** |
| **Causes** | • **autoimmune disease**: e.g. systemic lupus erythematosus<br>• neoplasia: e.g. lymphoma, CLL<br>• drugs: e.g. methyldopa | • neoplasia: e.g. lymphoma<br>• **infections**: e.g. mycoplasma, EBV |
| **treatment** | steroids, immunosuppression and splenectomy. | respond less well to steroids |

**Cold agglutinin disease**

- caused by autoantibodies that react at temperatures < 37 °C,
- typical causes are:
  - lymphoproliferative disorders,
  - infections such as mycoplasma or Epstein–Barr virus.
  - Around 50% of cases are idiopathic.
  - **Non-Hodgkin's lymphoma is more typically associated with cold agglutinins than Hodgkin's.**

**EX**: A 32-year-old man was prescribed an **oral antibiotic** for a **UTI**, **2 days later** he noticed that **his urine was increasingly dark in colour** with tinge of jaundice.

Lab: ↓**Hg** = 8.5 g/l. ↑**Reticulocytes** = 147 ×109/L (N= 25-85), Blood film: marked anisopoikilocytosis and bite cells.

What is the most likely diagnosis >>> **AIHA**

**Paroxysmal cold haemoglobinuria (PCH)** is a **rare** type of autoimmune haemolytic anaemia (AIHA) occurring primarily in **children/adolescent**.

The classic symptom of PCH is a sudden onset of haemoglobinuria following **exposure to cold, even for a few minutes**.

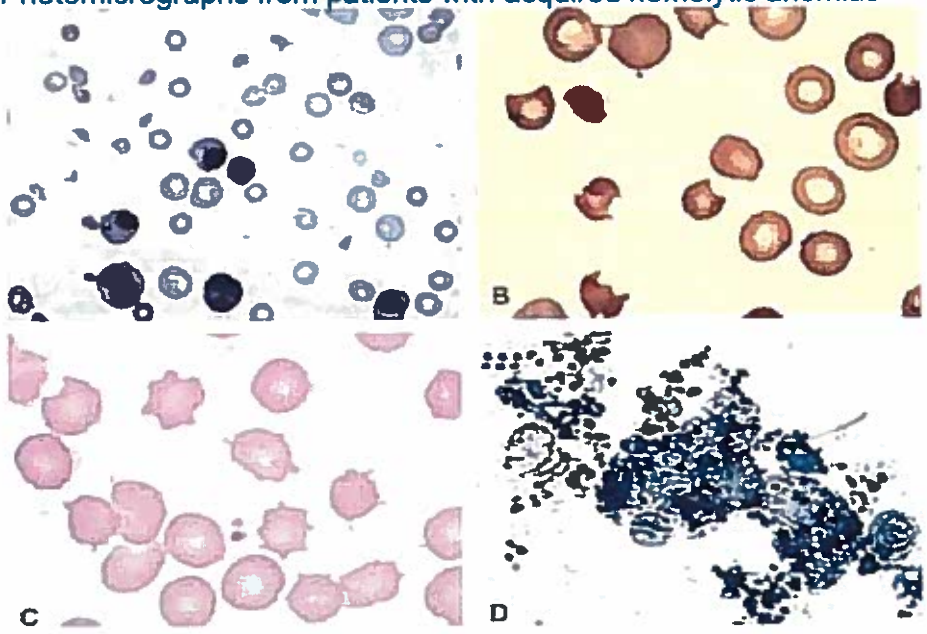
Symptoms may occur minutes to hours following exposure to cold.

The **direct agglutination test** (DAT) (**Coomb's** test) is usually **negative**.

Haemoglobinuria is not always present because in some persons with PCH the autoantibody level is not high enough to cause intravascular haemolysis.

PCH is usually of abrupt onset in the setting of an infectious disease.

Photomicrographs from patients with acquired hemolytic anemias




- **A**, Red cell fragmentation and nucleated red blood cells indicating microangiopathic hemolytic anemia caused by thrombotic thrombocytopenic purpura (TTP) (X400).
- **B**, Bite cells caused by severe drug-induced oxidant hemolysis (X1000).
- **C**, Spur cells from a patient with advanced liver cirrhosis (X1000).
- **D**, Urinary hemosiderin stained with Prussian blue (X400) resulting from intravascular haemolysis in a patient with paroxysmal nocturnal hemoglobinuria (PNH).

## G6PD Deficiency (Glucose-6-phosphate dehydrogenase deficiency)

G6pd deficiency is **the commonest red cell enzyme defect.**

↓ G6PD → ↓ glutathione → increased red cell susceptibility to oxidative stress

- It is more common in people from Mediterranean, Africa, Afro-Caribbean, Iraqi, Jew, South East Asian and **Chinese.**
- It is inherited **as X-linked recessive** fashion, so **males** are mostly affected (No male-to-male transmission).
- It predisposes to a hemolytic anemia reaction with drugs or infection.
- The hemolytic anemia is non-immune so direct antiglobulin test (DAT) will be negative.

- Many drugs can precipitate a crisis as well as infections and broad (fava) beans.
- **Treatment** revolves around avoidance of all known precipitating factors, and blood product support should only be given in unstable, symptomatic patients.

## Features:

- Neonatal jaundice.
- Intravascular haemolysis
- **RBCs Heinz bodies on blood film** (oxidised denatured haemoglobin).
- gallstones are common
- splenomegaly may be present

## Diagnosis: G6PD enzyme assay

- levels should be checked around 3 months after an acute episode of hemolysis, RBCs with the most severely reduced G6PD activity will have hemolyzed → reduced G6PD activity → not be measured in the assay → false negative results

## Treatment

- avoidance exposure to an oxidative stressor in the form of an infection, oxidative drug, or fava beans
- Acute hemolysis is self-limited, but in rare instances it can be severe enough to warrant a blood transfusion
  - Hemolysis typically occurs 24 to 72 hours after ingestion, with resolution within 4 to 7 days.
- **Methaemoglobinaemia in G6PD-deficient patients is best treated with exchange transfusion.**

## Drugs causing hemolysis in G6PD PATIENTS (5):

**CLUE:** DRUGS TO TREAT MALARIA AND UTI

- **Aspirin.**
- **Anti-malarial:** Primaquine, Quinine/quinidine, Chloroquine.
- Sulpha- **group drugs: Sulphonamides, Sulfamethoxazole, Sulphasalazine, Sulfonylureas.**
- **Ciprofloxacin.**
- **Nitrofurantoin**

## Safe drugs:

- Penicillin and derivatives.
- Cephalosporins
- Macrolides
- Tetracyclines
- Trimethoprim

In "Co-trimoxazole": the sulfamethoxazole causes hemolysis in G6PD, not the trimethoprim.

**EX:** Male boy 16 years old with acute abdomen, jaundice, fever, anemia with Hb 6, high LDH 1500 >>>? G6PD deficiency.
**EX:** A **62**-year-old Caribbean man with new onset type 2 DM presents to the ER. He has increasing lethargy and tiredness since starting a sulphonylurea a few days earlier.
On examination he has jaundiced sclerae, his BP is 135/72 mmHg, and pulse is 95. His mucous membranes look a little pale.
Lab: Hb=10, Bilirubin = 80 µmol/L (N <17), Heinz bodies in peripheral film.
The most likely diagnosis is **G6PD deficiency.**

**EX:** A **60**-year-old Chinese man has been started by his GP on quinine for leg cramps. He presents, a week later, with 5 days of darkened urine and 2 days of increasing breathlessness, back pain and fatigue.
Lab: Hb of **70** g/L (130-180) and raised reticulocyte count.
The best to explain this drug reaction **>>> G6PD.**

**EX:** Pt take Dapsone for malaria prophylaxis before trip to Kenya, the presented with confusion, tachypnea, desaturation, tachycardia, hypotension, anaemia HB 8, ↑RTX >>>> the diagnosis is that of **methaemoglobinaemia secondary** to **Dapsone** in a patient with underlying (**G6PD**) deficiency >>> **Treatment: Exchange blood transfusion.**
Methaemoglobinaemia in G6PD-deficient patients is best treated with **exchange transfusion.**

## Anemia of chronic disease

**Anaemia of inflammation:** is associated with chronic inflammatory

- status such as (inflammatory bowel disease, rheumatoid arthritis, chronic infections and malignancy) mediated through increased level of interleukin-6 which cause increase in hepcidin level which is negative ferroportin regulator, which results in reduced iron uptake in the gut and iron transfer from macrophages to erythroid progenitor cells in the bone marrow, and thus iron is low here.

**Anaemia of organ failure:**

- Can occur in renal, hepatic and endocrine gland failure Anaemia occur duo to reduced signal for red cell production.Iron level is normal except in renal failure duo to reduced degradation of hepcidin.

## Anaemia of older people:

- Present in up to 20% of older people more than 85 years old in whom a thorough evaluation for explanation of anaemia is negative. But remember to follow them thoroughly because some of them is duo **to clonal cytopenia of undetermined significance** which can turn to be myelodysplastic syndrome.

## Investigations

- RBCs morphology
  - normochromic, normocytic anemia.
- Reticulocyte count
  - ↓reticulocyte count points to ↓RBC production as the primary mechanism responsible for anemia,
- ↑ ferritin
- ↓ serum iron
- ↓ TIBC, transferrin saturation, and MCV

## Treatment

- treatment of the underlying disease.
- If underlying disease is unknown or treatment of underlying disease does not improve symptomatic anemia
  - measure EPO
    - if low, administer EPO or erythropoiesis-stimulating agents (ESAs)
      - make sure iron stores are sufficient
      - if insufficient, patients may be resistant to EPO
  - if normal, give packed RBCs

# Macrocytic anemia

Macrocytic anemia can be divided into causes associated with a Megaloblastic bone marrow and those with a normoblastic bone marrow.

| Megaloblastic causes | Normoblastic causes |
|---|---|
| • **Vitamin B12 deficiency**<br>• **Folate deficiency** | • Alcohol<br>• Liver disease<br>• Hypothyroidism<br>• Pregnancy<br>• Reticulocytotic<br>• Myelodysplasia<br>• Drugs: cytotoxics (methotrexate & azathioprine) |

# Vitamin B12 deficiency

Vitamin B12 is mainly used in the body for red blood cell development and also maintenance of the nervous system.
It is absorbed after **binding** to **intrinsic factor (IF)** (secreted from **parietal** cells in the stomach) and is **actively absorbed in** the terminal ileum.
A small amount of Vit. B12 is passively absorbed without being bound to IF.

**Hepatic stores of vitamin B12 can last for up to 5 years**, so it is not uncommon for vegans to display vitamin B12 deficiency years after starting their diet

## Causes of vitamin B12 deficiency:

- **Dietary** deficiency of Vit B12: like **vegetarians**, Vit B12 is only found in foods of animal origin e.g., meat, fish and eggs.
- Pernicious anemia
- Post gastrectomy
- Disorders of terminal ileum (site of absorption): Crohn's, blind-loop etc.

## Features of vitamin B12 deficiency:

- Macrocytic anemia
- Sore tongue and mouth
- Neuropsychiatric symptoms: e.g., Ataxia, Mood disturbances. The dorsal column is usually affected first (joint position, vibration) prior to distal paresthesia

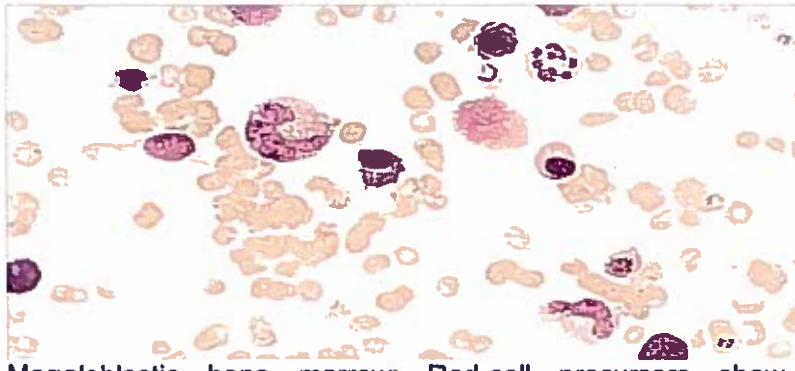
## Investigations for the pernicious anemia:

- **Anti-gastric parietal cell Ab** (**most common** found in 90% of cases but less specific).
- **Anti-Intrinsic factor Ab** (found in 50% but **specific** for pernicious anaemia).
- Macrocytic anaemia (↑ MCV)
- Pancytopenia (with ↓TLC, ↓ Plat.)
- ↑LDH may be raised due to **ineffective erythropoiesis.**
- ↓ serum vitamin B12
- ↓ serum folic acid
- Hypersegmented polymorphs on films, Megakaryocytes in bone marrow.
- Schilling test:
  - Radiolabelled Vit B12 is give on two occasion.
  - First on its own as I.M
  - Second with oral intrinsic factor
  - Measure urine B12

A **normal serum gastrin excludes** pernicious anemia (N < 55 pmol/l).

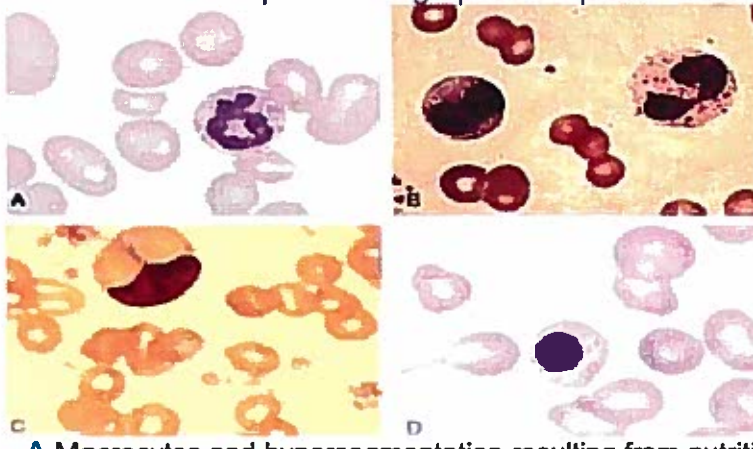
## Management:

- If no neurological involvement **1 mg of IM Hydroxocobalamin 3 times each week for 2 weeks, then once every 3 months.**
- If a patient has deficient in both **vitamin B12 and folic acid** then it is important to treat the **B12 deficiency first** to avoid precipitating subacute combined degeneration (SCD) of the cord.



Megaloblastic bone marrow: Red-cell precursors show a chromatin appearance like a sieve. There is a hypersegmented neutrophil and a giant metamyelocyte away from the center of the picture

Peripheral blood smear photomicrographs from patients with macrocytic anemia.




- **A.**Macrocytes and hypersegmentation resulting from nutritional megaloblastic anemia.
- **B,** Bilobed neutrophil (Pelger-Huét cell) and a metamyelocyte associated with myelodysplastic syndrome.
- **C,** Erythrophagocytosis and spurious macrocytosis caused by agglutinated red cells in a patient with Mycoplasma associated cold agglutinin hemolytic anemia.
- **D,** Nucleated and teardrop red cells associated with myelofibrosis.

# Sickle cell disease (SCD)

Sickle cell anemia (SSA) is characterized by periods of good health with intervening crises.
It is inherited as **autosomal recessive**.
It is caused by **mutation** in β globin chain of Hb, causing hydrophilic amino acid **glutamic acid** to be replaced with the hydrophobic amino acid valine at the 6th position.
The β globin gene is found on the short arm of **chromosome 11**.
The association of 2 wild type α globin subunits with 2 mutant β globin subunits → forms hemoglobin S **(Hb S)**.
**HbS** has a life span of **only 30 days** compared to the normal 120 days.

**HbS** has the following properties:

- It contains **two α**-like globins and **two β**-like globins and **four haem** molecules.
- It is the result of a **point mutation** substituting glutamate for **valine** at position **6 in chromosome 11 for beta chain.**
- It is **less negatively** charged, due to the loss of glutamate for valine.
- The loss of the negative charge and the configuration of HbS makes it **less soluble** than HbA.
- It has **lower affinity for oxygen** than HbA (**right**-shift of the oxygen-dissociation curve), which increases the risk of **desaturation**, but improves the yield of oxygen to the tissues.
- It polymerizes with adjacent HbS.

## Investigations

- definitive diagnosis of sickle cell disease is by haemoglobin electrophoresis

**Sickle cell disease** is **most common** in regions where **P.falciparum malaria** is endemic and in ethnic groups that have migrated from these areas. The sickle cell gene is most prevalent in areas where **malaria** is also prevalent. This genetic abnormality is not caused by malaria, but the selective advantage of the carrier state in malarial regions has allowed it to persist in the gene pool (positive selective evolutionary pressure).
Patients with **sickle cell trait** have just as **much risk** of contracting **P. falciparum malaria** compared with patients with HbAS or HbAA.
Patients with **HbSS** are at higher risk of **severe** malaria with complications and have a higher mortality rate.
However, the reduced red cell life cycle in HbAS reduces parasitaemia, which reduces the risk of severe disease and neurological complications (for example, seizures and coma).

## Types:

- **Sickle cell anaemia is a specific form of sickle cell disease** in which there is **homozygosity** for the mutation, it is also known as "Haemoglobin S", "Hb SS", "SS disease".
- **Heterozygous**: 1 sickle gene and 1 normal gene, it is known as "Hb AS" or "Sickle cell trait".
- **Other, rarer forms** of sickle cell disease in which there are compound heterozygous state in which the person has only one copy of the mutation that causes Hb S and one copy of another abnormal Hb allele. Examples:
  - "HbSC": (sickle –haemoglobin C disease).
  - "HbS/β+": (sickle-beta-plus-thalassemia).
  - "HbS/β0" : (sickle-beta-zero-thalassemia)

## Four main types of crises are recognised:

- Thrombotic, 'painful crises' (vaso-occlusive crises)
- Sequestration (spleen, liver, kidney or lungs)
- Aplastic (Parvovirus)
- Haemolytic

## Thrombotic crises = Painful crises or Vaso-occlusive crises:

- Precipitated by infection, dehydration, deoxygenation
- Infarcts occur in various organs including the bones (e.g. avascular necrosis of hip, hand-foot syndrome in children, lungs, spleen and brain.
- **Functional hyposplenism** in SCD also renders sufferers susceptible to infection with **encapsulated** bacteria (pneumococci, meningococci).
- Patients with sickle cell disease have a predisposition to develop **osteomyelitis** due to **Salmonella** species.

**Salmonella osteomyelitis** is seen in patients with sickle cell anaemia.

## Sequestration crises:

- Sickling within organs such as the spleen, liver, kidney or lungs causes pooling of blood with worsening of the anaemia
- **Acute chest syndrome**: dyspnea, chest pain, pulmonary infiltrates, low pO2 - the most common cause of death in **adult**. (Hydroxyurea ↓ incidence of acute chest syndrome).
- The most common cause of death in **childhood** is: infarction (CVS) and infection (pneumococcal, chlamydia, mycoplasma).
- 5-10% of sickle cell patients will suffer a stroke, usually during childhood. The risk can be predicted by transcranial Doppler measurement of middle cerebral artery (MCA) flow rate, and prompt institution of a prophylactic transfusion program to reduce the HbS %

can prevent further strokes. When **stroke** is occurred with lateralization >>> **Treatment**: **Exchange transfusion programme** (**NOT** thrombolytic therapy, **NOT** Hydroxyurea, **NOT** BMT).

**EX:** Pt. with sickle cell anaemia presents with abdominal pain + **splenomegaly**+ **anaemia** >>> so, It is a **Sequestration crises**.

**Acute chest syndrome:**

It is defined as a **'new infiltrate** consistent with consolidation at least segmental in size, **and one of**:

- **Chest pain,**
- **Fever,** a temperature > 38.5°C,
- **Shortness of breath** (tachypnoeic, wheezing, cough or low O2 sat).

It is important to remember that not all of the above features will be present at the same time, CXR changes often lag behind, i.e. CXR may be normal initially, and subsequent imaging will reveal an infiltrate.

The syndrome can develop because of infection, infarction or a combination of the two.

Although **lung new infiltrates in CXR** are a characteristic feature of acute chest syndromes, it is important to remember that they can lag behind, and treatment should not be delayed in the absence of CXR changes if all other clinical signs suggest acute chest syndrome.

The key is to have a high index of suspicion and monitor vital signs particularly oxygen saturations regularly and anticipate development of possible acute chest syndrome. Early recognition and treatment is lifesaving.

**Chest pain** is often a feature of acute chest syndrome, either from the onset or presents later during the course of disease.
**Shortness of breath** is an important feature of acute chest syndrome and one of the main markers of deterioration indicating the need for possible exchange transfusion.
**Fever,** usually temperature of greater than 38.5°C is another recognised feature of acute chest syndrome. All patients with temperatures more than 38°C should have cultures sent.

Acute chest syndrome is a combination of signs and symptoms, not all of them need to be present for a diagnosis to be made.

**Hydroxyurea** reduces the incidence of acute chest syndrome and the need for blood transfusion in people with SCD over a mean of 21 months.

## Aplastic crises:

- Caused by infection with **parvovirus B19.**
- The virus infects red cell progenitors in bone marrow, resulting in cessation of erythropoiesis and a **very rapid drop in haemoglobin.**
- **Sudden fall** in Hb **without an appropriate ↑reticulocytosis.**
- The condition is **self-limited**, with bone marrow recovery occurring in 7-10 days, **followed by brisk reticulocytosis.**

## Hemolytic crises:

- Rare
- Fall in haemoglobin due an increased rate of haemolysis

The mechanism of action of **hydroxycarbamide (Hydroxyurea)** in the setting of its use in **sickle** cell disease >>> **stimulating** the **production** of **fetal haemoglobin (Hb F)** which protects against sickling.
**Hydroxyurea is HbF switching therapy.**
It is **not** used in the **acute** setting.

A pregnant woman attends for her booking antenatal appointment. How will screening for sickle cell disease be undertaken?
**She will first be screened for sickle cell carrier status. If that test is positive, her partner will be screened, and only if both are positive and confirmed by genetic testing, she will be offered chorionic villus sampling (CVS) or amniocentesis.**

In low prevalence trusts laboratory screening is only carried out if the baby is identified as being at risk of a haemoglobinopathy based on the family origin questionnaire and a routine full blood count from the mother.
In **high prevalence trusts all** women undergo the **initial** laboratory **screening** to identify **if the mother carries** the sickle cell gene, regardless of family origin. However, the family origin questionnaire still needs to be completed to facilitate diagnosis of the type of haemoglobinopathy.
The **father** is tested for carrier status **only if** the mother is found to be a carrier.
If **both** are found to be carriers this is **confirmed by genetic testing** before offering chorionic villus sampling (**CVS**) (8-10 weeks) or **amniocentesis** (14-16 weeks).

The **anaemia** associated with sickle cell disease is usually **only symptomatic below 70 g/L**, as oxygen is released more readily from erythrocytes.

There is a tendency to **iron overload** in sickle cell disease and **therefore oral iron therapy is not usually indicated.**

A **urine concentrating defect** is quite common in sickle cell anemia.

The **spleen is decreased in size** after 6 months of age, due to repeated episodes of venoocculsion and infarction, and patients often have **functional hyposplenism (auto-splenectomy)** and so they are recommended to take **daily penicillin**.

SCD patients are at much higher risk from gall stones disease due to chronic hyperbilirubinaemia.

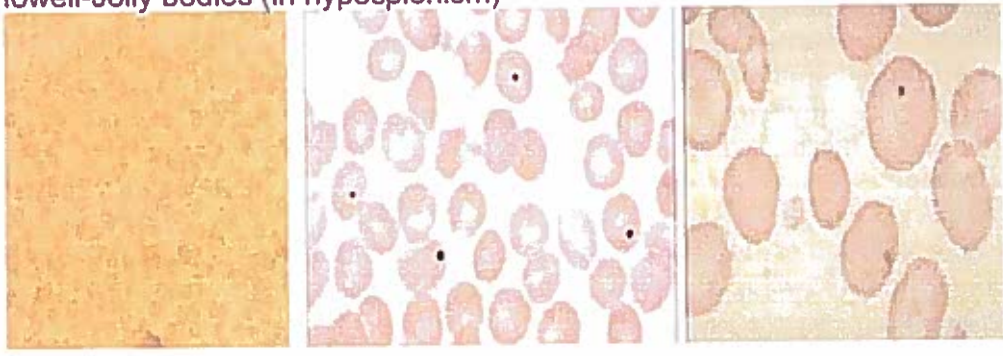
Intra-articular steroids have been associated with a sickle cell crisis, the mechanism of which is not fully understood, but they should be avoided. ☹

All adults who have **hyposplenism**, including patients with **SCD**, need:

- Yearly **influenza** vaccine.
- **Pneumococcal** C vaccine, (adults and children over 2 years) repeated every five years.
- **Haemophilus influenzae** type b; **if** not already given as part of childhood immunisation.
- **Conjugated meningococcal C vaccine**; **if** not already given as part of childhood immunisation.
- **Meningococcal ACWY vaccine**; if travelling to areas with high risk of meningitis.

Although patients with sickle cell disease do need the **yearly influenza** vaccination, they also need **five yearly Pneumovax**.

Howell-Jolly bodies (in hyposplenism)



- Hawell-Jolly bodies are intracellular inclusion bodies consisting of remnants of DNA.
- These are spherical bluish inclusions within erythrocytes and are nuclear fragments of condensed DNA which are normally removed by the spleen.
- They are seen in: severe haemolytic anaemias or in hyposplenic/asplenic patients like in splenectomy.

# Hereditary spherocytosis (HS)

- **The most common hereditary hemolytic anemia in people of northern European descent important if you are going to set for the exam in UK**
- **Autosomal dominant** defect of red blood cell cytoskeleton (usually the spectrin component) causing spherocytes in blood film.
- The normal biconcave disc shape is replaced by a sphere-shaped RBC
- ↓ RBCs survival as destroyed by the spleen.
- Hereditary spherocytosis is usually an incidentally detected condition unless the person has active **hemolysis**, **gall stones** or uncomfortable **splenomegaly**. In this situation, which is not uncommon, the presentation is with gall stones.

## Presentation:

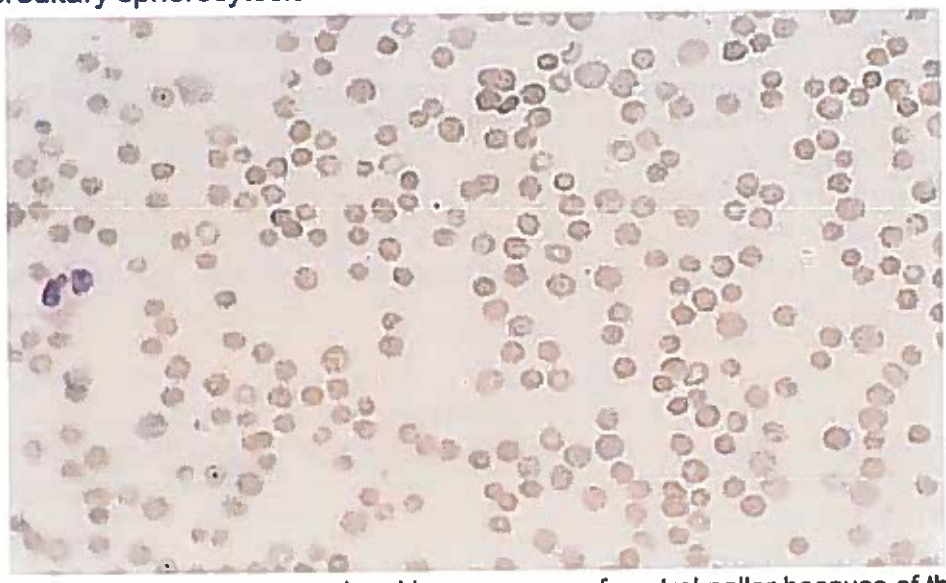
- Failure to thrive
- **Jaundice, gallstones**
- **Splenomegaly**
- **Aplastic crisis** precipitated by **parvovirus** infection
- Degree of hemolysis variable
- **↓low MCV & MCH, ↑high MCHC** (due to hyperdense cells), ↑LDH, **↑Unconjugated bilirubin, ↑ RTX, ↓ Haptoglobin.**
- Direct Coombs test (DCT) is negative. As it is not an immune hemolysis.

## Diagnosis:

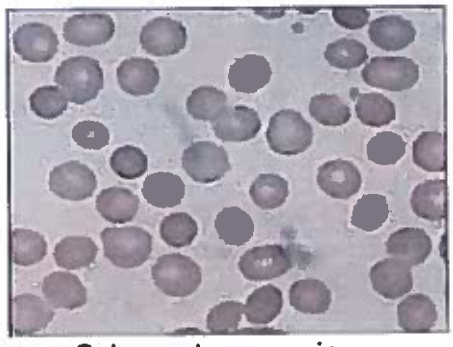
- **Osmotic fragility test:** (Rupture of Spherocytes in mildly hypotonic solution), but this has now been replaced by the **eosin-5-maleimide** binding to red cells and then being detected by flow cytometry.

The osmotic fragility test is unreliable and is **no longer recommended in routine clinical practice.** Osmotic gradient ektacytometry is used to differentiate hereditary spherocytosis from hereditary stomatocytosis, but is only available in specialised laboratories.
If the diagnosis is equivocal, the cryohaemolysis test and EMA binding can be used.
In atypical cases, gel electrophoresis analysis of erythrocyte membranes is the test of choice.

## Hereditary spherocytosis



- Spherocytes are round and have no area of central pallor because of their spherical shape.
- They are rather smaller than the on-spherocytic normal cells.
- There is some polychromasia as well due to reticulocytosis.



- Spherocytes: seen in
  - Hereditary spherocytosis.
  - Autoimmune hemolytic anemia.

- Schistocytes ('helmet cells'):
  - Intravascular hemolysis.
  - Mechanical heart valve
  - DIC.

### Management:

- Folate replacement
- **Splenectomy**: it should be performed after the age of 6 years and with appropriate counselling about the infection risk.

It is important to rule out stomatocytosis where splenectomy is contraindicated because of the thrombotic risk.

**Comparing G6PD deficiency to hereditary spherocytosis:**

| | G6PD deficiency | Hereditary spherocytosis |
|---|---|---|
| Gender | Male (X-linked recessive) | Male + female (autosomal dominant) |
| Ethnicity | Mediterranean + African | Northern European |
| Typical history | • Neonatal jaundice.<br>• Infection/drugs precipitate hemolysis.<br>• Gallstones. | • Neonatal jaundice.<br>• Chronic symptoms although hemolytic crises may be precipitated by infection.<br>• Gallstones.<br>• Splenomegaly is common. |
| Blood film | **Heinz bodies** | **Spherocytes** (round, lack of central pallor) |
| Diagnostic test | Measurement G6PD enzyme activity | Osmotic fragility test<br>Eosine 5-maleimide flow cytometry |

**Ex:** The clue of hereditary spherocytosis >> by the normocytic anemia, gallstones and family history.

**EX:** Pt with **hereditary spherocytosis + acute abdomen** >> think of: **Biliary colic** or **rupture spleen.**

**NB:** Red cell membrane defects are broadly classified into hereditary spherocytosis (HS), hereditary elliptocytosis (HE) and others.

**Horizontal** membrane protein defects (for example, spectrin ankyrin interaction defect) results in **HE** whereas vertical defects result in hereditary spherocytosis.

**Elliptocytosis** is usually caused by **spectrin** and spectrin-protein 4.1 defects.

**Heterozygotes are asymptomatic but show elliptocytes on blood film; they do not have hemolysis and do not require any particular treatment.**

| G6PD deficiency | | Hereditary spherocytosis |
|---|---|---|
| Male (X-linked recessive) | Inherited haemolytic anaemia | Male + female (autosomal dominant) |
| African + Mediterranean descent | Neonatal jaundice | Northern European descent |
| Intravascular haemolysis | Gallstones | Extravascular haemolysis |
| Certain drugs may precipitate haemolysis | Infection may precipitate haemolysis | |
| Heinz bodies | | |

## Cryoglobulinaemia

Immunoglobulins which undergo reversible precipitation at 4 deg C, dissolve when warmed to 37 deg C. One-third of cases are idiopathic

### Three types

- type I (25%): monoclonal
- type II (25%): mixed monoclonal and polyclonal: usually with rheumatoid factor
- type III (50%): polyclonal: usually with rheumatoid factor

**Type I**

- monoclonal - IgG or IgM
- associations: multiple myeloma, Waldenstrom macroglobulinaemia

**Type II**

- mixed monoclonal and polyclonal: usually with rheumatoid factor
- associations: **hepatitis C**, rheumatoid arthritis, Sjogren's, lymphoma

**Type III**

- polyclonal: usually with rheumatoid factor
- associations: rheumatoid arthritis, Sjogren's

**Symptoms** (if present in high concentrations)

- **Raynaud's only seen in type I**
- cutaneous: vascular purpura, distal ulceration, ulceration
- arthralgia
- renal involvement (diffuse glomerulonephritis)

### Tests

- low complement (esp. C4)
- high ESR

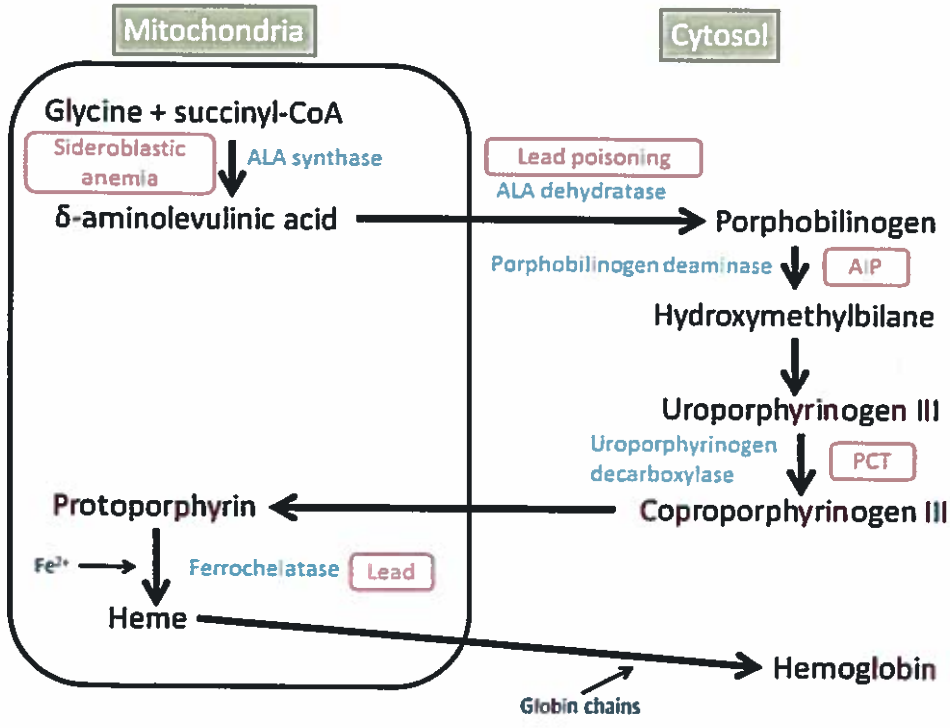
### Treatment

- immunosuppression
- plasmapheresis

## Porphyrias

### Overview

- abnormality in enzymes responsible for the biosynthesis of haem
- results in overproduction of intermediate compounds (porphyrins)
- may be acute or non-acute




### Acute intermittent porphyria (AIP)

- autosomal dominant
- defect in porphobilinogen deaminase
- female and 20-40 year olds more likely to be affected
- typically present with abdominal symptoms, neuropsychiatric symptoms
- hypertension and tachycardia common
- urine turns deep red on standing

### Porphyria cutanea tarda (PCT)

- most common hepatic porphyria
- defect in uroporphyrinogen decarboxylase
- may be caused by hepatocyte damage e.g. alcohol, oestrogens
- classically photosensitive rash with bullae, skin fragility on face and dorsal aspect of hands
- urine: elevated uroporphyrinogen and pink fluorescence of urine under Wood's lamp
- manage with chloroquine

### Variegate porphyria

- autosomal dominant
- defect in protoporphyrinogen oxidase
- photosensitive blistering rash
- abdominal and neurological symptoms
- more common in South Africans

## Acute intermittent porphyria in details

Acute intermittent porphyria (AIP) is a rare autosomal dominant condition caused by a defect in porphobilinogen deaminase, an enzyme involved in the biosynthesis of haem.
The results in the toxic accumulation of delta aminolaevulinic acid and porphobilinogen.
It characteristically presents with abdominal and neuropsychiatric symptoms in 20-40-year-olds. AIP is more common in females (5:1)

### The classical presentation is a combination of abdominal, neurological and psychiatric symptoms:

- abdominal: abdominal pain, vomiting
- neurological: motor neuropathy
- psychiatric: e.g. depression
- hypertension and tachycardia common

### Diagnosis

- classically urine turns deep red on standing
- raised urinary porphobilinogen (elevated between attacks and to a greater extent during acute attacks)
- assay of red cells for porphobilinogen deaminase
- raised serum levels of delta aminolaevulinic acid and porphobilinogen

## Management

- avoiding triggers
- acute attacks
  - IV hematin/hem arginate
  - IV glucose should be used if hematin/hem arginate is not immediately available

## Acute intermittent porphyria: drugs

| Drugs which may precipitate attack | | Safe Drugs |
|---|---|---|
| • Alcohol<br>• Barbiturates<br>• Benzodiazepines<br>• Tricyclic antidepressants<br>• Halothane<br>• Oral contraceptive pill<br>• Sulphonamides<br>• Cephalosporins<br>• Erythromycin<br>• Isoniazid<br>• flucloxacillin<br>• Anabolic steroids | • Sulphonylureas<br>• Theophylline<br>• Antihistamines<br>• MAOIs<br>• Amiodarone<br>• Simvastatin.<br>• **Diuretics**<br>• **calcium channel blockers**<br>• ACE inhibitors | • Paracetamol<br>• Aspirin<br>• Ibuprofen<br>• Codeine<br>• Morphine<br>• Chlorpromazine<br>• β-blockers<br>• Gabapentin<br>• Penicillin<br>• Metformin<br>• amoxicillin |

**Treatment of seizures in AIP >> Gabapentin**

## Treatment:

- **decrease the activity of delta-aminolevulinic acid synthase (ALA)**
  **glucose** (carbohydrate loading)
    - high-glucose diets or infusions have been used for mild attacks of pain without neurological symptoms

  **intravenous haem arginate**
    - thereby decreasing heme precursor synthesis.
    - The treatment of choice
    - opiate analgesia.

# Assessment of anemia

# Polycythemia

Polycythemia may be relative, primary (polycythemia rubra Vera) or secondary.

| Relative causes (Pseudo-polycythemia) | Primary | Secondary causes (due to ↑ EPO) |
|---|---|---|
| • **Dehydration**<br>• Stress: Gaisbock syndrome | PRV | • **COPD**<br>• **Obstructive sleep apnoea**<br>• **High attitude.**<br>• **Excessive erythropoietin (Erythropoietin-secreting tumours):**<br>  ○ Cerebellar hemangioma,<br>  ○ **Hypernephroma**,<br>  ○ Hepatoma (**HCC**),<br>  ○ **Uterine fibroids** (as it may cause menorrhagia which in turn leads to blood loss - polycythemia is rarely a clinical problem). |

To differentiate between true (primary or secondary) polycythaemia and relative polycythemia **red cell mass** estimation with **51 Cr radiolabeled Chromium** is sometimes used, it isn't so easy to obtain.

In true polycythemia: ↑ **Red cell mass** (N=1312-2187 ml), ↑ **Haematocrit**, **low-normal plasma volume** (N= 2362-3938 ml).

In **true** polycythaemia **the total red cell mass** in males > 35 ml/kg and in women > 32 ml/kg.

In **secondary** polycythemia as a consequence of respiratory diseases or renal cell carcinoma is characterized by **high levels of circulating plasma EPO driving erythropoiesis** (Normal serum EPO is up to 20 mU/ml).

The discovery of the **JAK2 mutation** has made red cell mass a second-line investigation for patients with suspected JAK2-negative PRV.

JAK2 is a crucial tyrosine kinase which transmits the EPO signal to increase red cells production.

The **most specific** with respect to **confirming** the diagnosis of primary polycythaemia (PRV) **versus** a diagnosis of secondary polycythemia is >>> **JAK2 mutation screening** **and splenomegaly with normal arterial oxygen saturation. There is usually elevated WBCs and platelet count.**
**Polycythemia rubra Vera (PRV)** >>> **JAK2 mutation.**

**Von Hipple Lindau syndrome**: is **autosomal dominant** condition, it is a **secondary** polycythemia, it can lead to **retinal** and **CNS tumours** as well as **pheochromocytoma**. **Death** is often due to **renal cell carcinoma**. A proportion of **cerebellar hemangiomas** secretes erythropoietin-like substance, leading to a **secondary** polycythemia.

**EX**: Female 55 years old, **dizziness, Hb 22, Nystagmus, ataxia, broad-based gait, dilated retinal veins on fundoscopy >>> Von Hipple Lindau syndrome.**

## Polycythemia rubra Vera (PRV)

PRV is a **myeloproliferative disorder** caused by clonal proliferation of a marrow stem cells (erythroid, myeloid and megakaryocytic elements) leading to a ↑ **RBCs**, **often accompanied by overproduction of neutrophils and platelets.**

It has peak incidence in the **sixth decade**, with typical features including hyperviscosity, pruritus and splenomegaly.

It has an incidence of 5-17/million population/year.

It has recently been established that a **mutation in JAK2** is present in approximately **95%** of patients with **PRV** and this has resulted in significant changes to the diagnostic criteria.

Eventual transformation of primary polycythemia (PRV) may occur to AML, CML and CLL.

### Features:

- **Hyperviscosity:** (**headache, tinnitus, visual disturbance, arterial and venous thrombosis, stroke like limb weakness, TIA, Budd-Chiari syndrome, portal vein thrombosis, angina, intermittent claudication**)
- **Pruritus**, typically after a hot bath
- **Splenomegaly**
- Hemorrhage (secondary to abnormal platelet **function** NOT NUMBER)
- Plethoric appearance
- Hypertension in a third of patients
- **Low ESR**
- **Raised leukocyte ALP.**

- **Mild prolonged PT & PTT:** this is related to the ratio of plasma and citrate. In the blue tubes that are used for coagulation tests the ratio is normally 1 citrate to 9 of whole blood. If there is less plasma due to the polycythaemia there will be excess citrate and this will prolong coagulation tests such as the APTT and prothrombin time.
- Others: **hyperuricemia**, peptic ulceration.

**Following history and examination, the British Committee for Standards in Haematology (BCSH) recommend the following tests are performed:**

- CBC/film (raised hematocrit; **neutrophils**, basophils, **platelets** raised in half of patients)
- JAK2 mutation
- Serum ferritin
- Renal and liver function tests

**If the JAK2 mutation is negative and there is no obvious secondary causes the BCSH suggest the following tests:**

- Red cell mass
- Arterial oxygen saturation
- Abdominal ultrasound
- ↓ Serum erythropoietin level
- Bone marrow aspirate and trephine
- Cytogenetic analysis
- Erythroid burst-forming unit (BFU-E) culture

The diagnosis of PRV is based on the revised WHO criteria.

**Diagnosis** requires two major criteria and one minor criterion, or the first major criterion and two minor criteria.

**Major criteria:**

- **Hemoglobin** of more than 185 g/L in men, 165 g/L in women, or **elevated red cell mass** > 25% above mean normal predicted.
- Presence of **JAK 2 mutations**, commonly 617V F

**Minor criteria:**

- **Bone marrow biopsy** showing hypercellularity with prominent erythroid, granulocytic and megakaryocytic proliferation
- **Serum EPO below** normal range
- Endogenous erythroid colony formation in vitro.

Oxygen saturations, splenic size, platelet count and white cell count no longer feature in the diagnostic criteria.

**The diagnostic criteria for PRV** have recently been updated by the BCSH. This replaces the previous PRV Study Group criteria.

**JAK2-positive PRV**: diagnosis requires both criteria to be present:

| | |
|---|---|
| A1 | High haematocrit (>0.52 in men, >0.48 in women) OR raised red cell mass (>25% above predicted) |
| A2 | Mutation in JAK2 |

**JAK2-negative PRV**: diagnosis requires A1 + A2 + A3 + either another A or two B criteria:

| | |
|---|---|
| A1 | Raised red cell mass (>25% above predicted) OR haematocrit >0.60 in men, >0.56 in women |
| A2 | Absence of mutation in JAK2 |
| A3 | No cause of secondary erythrocytosis |
| A4 | Palpable splenomegaly |
| A5 | Presence of an acquired genetic abnormality (excluding BCR-ABL) in the haematopoietic cells |
| B1 | Thrombocytosis (platelet count >450 * $10^9$/l) |
| B2 | Neutrophil leucocytosis (neutrophil count > 10 * $10^9$/l in non-smokers; > 12.5*$10^9$/l in smokers) |
| B3 | Radiological evidence of splenomegaly |
| B4 | Endogenous erythroid colonies or low serum erythropoietin |

## Differential diagnosis:

- Spurious polycythemia.
- Secondary polycythemia :hypoxia induced or epo- secreting tumors, or abnormal hemoglobin.

## Management:

- **Venesection** - first line treatment, it will lessen the rates of thrombotic complications but there is no evidence that venesection improves long term survival rates.
- Aspirin
- Hydroxyurea -slight increased risk of secondary leukaemia
- Phosphorus-32 therapy

## Prognosis:

- **Thrombotic events** are a significant cause of morbidity and mortality.
- 5-15% of patients progress to **myelofibrosis.**
- 5-15% of patients progress to **acute myeloid leukaemia** (AML) (risk increased with chemotherapy treatment).

The most common types of transformations seen in patients with polycythemia rubra Vera >> **myelofibrosis** and **AML.**

## Myeloproliferative disorders

- Polycythaemia rubra Vera (PRV).
- Essential Thrombocythemia (ET).
- AML and CML.
- Myelofibrosis.

**For:**

- **Bone marrow cytogenetic.**
- Peripheral blood **molecular analysis** (PCR): BCR-ABL translocation (t[9:22]) in CML.
- Peripheral blood **Immunophenotyping**.

## Haemochromatosis

Haemochromatosis is an **autosomal recessive** disorder of iron absorption and metabolism resulting in iron accumulation.

It is caused by inheritance of mutations in the **HFE gene** on both copies of **chromosome 6.** (There are rare cases of families with classic features of genetic haemochromatosis but no mutation in the HFE gene).

Haemochromatosis is **the most prevalent genetic condition in Caucasian** population, with a carrier rate of 1 in 10 and is present in about 1 in 200-400 people.

Cystic fibrosis (CF) has a carrier rate of 1 in 25 and is present in about 1 in 2500 births So, **CF** is often considered as **the most common lethal inherited condition in Caucasians.**

**So haemochromatosis is more common than cystic fibrosis.**

There is continued debate about the best investigation to **screening** for haemochromatosis. The 2000 BCSH guidelines suggest:

- **General population: Transferrin saturation** is considered the most useful marker. **Ferritin** should also be measured but is not usually abnormal in the early stages of iron accumulation.
- **Testing family members: genetic testing for HFE mutation.**
- These guidelines may change as HFE gene analysis become less expensive.

**Haemochromatosis screening:**

- General population: Transferrin % > Ferritin.
- Family members: HFE genetic testing.

## Presenting features:

- Often asymptomatic in early disease and initial symptoms often non-specific e.g., lethargy, **erectile dysfunction**, **arthralgia/arthritis often of the hands** esp. the 2nd and 3rd metacarpo-phalangeal joints.
- **Bronze skin pigmentation** (Skin pigmentation rather than a rash).
- **DM.**
- **Liver**: stigmata of chronic liver disease, hepatomegaly, cirrhosis, hepatocellular deposition.
- **Cardiac** failure (secondary to **DCM**).
- Hypogonadism **(secondary to cirrhosis and pituitary dysfunction Hypogonadotropic hypogonadism).**

| Reversible complications | Irreversible complications |
|---|---|
| • Cardiomyopathy<br>• Skin pigmentation | • Arthropathy<br>• DM<br>• Liver cirrhosis<br>• hypogonadotropic hypogonadism |

**Both** males and females are affected equally, but females are often 'protected' from the clinical features by menstrual blood loss.

**Early** diagnosis and treatment is critical in haemochromatosis as survival and morbidity are improved if phlebotomy is initiated prior to the development of cirrhosis.

**Transferrin saturation** is suggested as the initial screening test: a level of more than 45% warrants further investigation (less than 45% usually excludes the diagnosis). Genetic screening is then performed. If the usual C282Y HFE mutation is found this makes the diagnosis.

If the C282Y HFE mutation is not present other genotypes should be looked for and if present a liver biopsy is indicated.

**Ferritin** is measured to help guide further investigation and treatment: **if more than 1000** >>> a **liver biopsy** should be performed and treatment initiated.

If the ferritin is within normal range and the liver function tests are normal patients can be followed closely.

## Diagnostic tests:

- Molecular genetic testing for the C282Y and H63D mutations
- Liver biopsy: Perl's stain

## Typical iron study profile in patient with haemochromatosis:

- ↑ Iron.
- **Low** TIBC.
- ↑ Ferritin (e.g. > 500 ug/l) and
- ↑ Transferrin saturation **> 55%** in men or **> 50%** in women.

## Treatment:

The goal of therapy is to remove excess body iron stores which is commonly done via **phlebotomy**. Initially this is **weekly** or **twice weekly** (if tolerated) venesections of 500 $cm^3$ until the serum ferritin is less than 50 ng/mL. Transferritin saturation should also be reduced to less than 50% if possible.

Monitoring adequacy of venesection: BSCH recommends:

**Transferrin saturation** should be kept below **50%** and the serum **ferritin** concentration below **50 ug/l.**

After these goals are reached maintenance therapy is typically required three to four times per year. **When iron overload and anemia are present concomitantly chelation with deferoxamine may be required.**

Patients should be told to avoid vitamin C supplementation as this can enhance iron toxicity.

End stage liver disease, portal hypertension and hepatocellular carcinoma (which is increased up to 200-fold) may necessitate liver transplantation.

**N.B:** Joint x-rays characteristically show **chondrocalcinosis**.

**EX:** A 36-year-old male with Type 1 DM of 3 years duration presented with decreased libido and erectile dysfunction since diagnosis. No abnormalities were noted on genital examination. Lab: with **low testosterone** and **low FSH** >>> **Haemochromatosis** >>> Check serum **ferritin.**

# Neutropenia

It is defined as an absolute peripheral blood neutrophil count of $<2x10*10^9$ /L.

There is a racial variation: black and Middle Eastern people may have neutrophil count of $< 1.5x10*10^9$ /L normally.

**Neutropenia may be further subdivided as follows:**

| Severity | Neutrophil count |
|---|---|
| Mild | 1.0 - 1.5 * $10^9$ |
| Moderate | 0.5 - 1.0 * $10^9$ |
| Severe | < 0.5 * $10^9$ |

## Congenital neutropenia:

- Kostmann's syndrome
- Chediak-Higashi syndrome
- Schwachmann-Diamond syndrome
- Cyclical neutropenia

## Acquired neutropenia:

- **Infection**: viral: influenza, HIV, hepatitis and Bacterial sepsis.
- **Drugs**: phenytoin, carbimazole, chlorpromazine, cotrimoxazole, ACEI.
- **Immune-mediated**: SLE, Felty's syndrome (RA + splenomegaly + neutropenia).
- **Haematological malignancy**
  - myelodysplastic malignancies
  - aplastic anemia
- Rheumatological conditions
- Systemic lupus erythematosus: mechanisms include circulating antineutrophil antibodies
- Rheumatoid arthritis: e.g. hypersplenism as in Felty's syndrome
- Severe sepsis
- Hemodialysis

## Investigations:

- Blood film.
- Haematinics: factors that ↑ Hb (Fe, TIBC, Vit B12, Folic acid, Vit D).
- Autoimmune profile.
- Bone marrow aspirate/trephine: if there is severe or prolonged neutropenia or features suggestive of bone marrow failure.

# Neutropenic sepsis (Febrile neutropenia)

Neutropenic sepsis is a relatively common complication of cancer therapy, usually as a consequence of chemotherapy.

It may be defined as a **neutrophil count of < 0.5 * $10^9$** in a patient who is having anticancer treatment and has one of the following:

- A temperature higher than 38°C or
- Other signs or symptoms consistent with clinically significant sepsis.

## Causes

**Neutropenic patients should avoid cold meats, soft cheese and dairy products due to risk of listeriosis**

**Mucositis can be a source of neutropenic sepsis >> Swab mouth ulcer**

## Prophylaxis:

- If it is anticipated that patients are likely to have a neutrophil count of < $0.5 * 10^9$ as a consequence of their treatment they should be offered a **fluoroquinolone.**

## Management:

- Antibiotics must be started immediately, **do not wait for the WBC**
- NICE recommend starting empirical antibiotic therapy with piperacillin with **tazobactam (Tazocin) immediately.**
- Many units **add vancomycin** if the patient has central venous access but NICE do not support this approach.
- Following this initial treatment patients are usually assessed by a specialist and risk-stratified to see if they may be able to have outpatient treatment.
- If patients are still febrile and unwell after 48 hours **an alternative antibiotic such as meropenem is often prescribed +/- vancomycin.**
- If patients are not responding after 4-6 days the Christie guidelines suggest ordering **investigations for fungal infections** e.g. HRCT, Aspergillus PCR etc. to determine the likelihood of systemic fungal infection, **rather than just starting therapy antifungal therapy blindly**. (For the purposes of the exam however the answer is often to give antifungals empirically).
- There **may** be a role for **G-CSF** in **selected** patients.

**Neutropenic sepsis treatment >>> Tazocin + Gentamycin ± Vancomycin ± Antifungal**

**EX:** In **AML** (TLC **250,000**, Hb 5, PLT 25,000) although the white cell count is **elevated**, functionally the patient is **still neutropenia** and the case should still be managed as **febrile neutropenia >>> Treatment: Fluid resuscitation** + blood and urine **cultures** followed by **piperacillin/tazobactam + gentamicin.**
**NB:** In patients who are **prone to invasive fungal infections** it is **no** longer suggested that empirical therapy with systemic antifungals is commenced (British Committee for Standards in Haematology guidelines).
**Serological** and/or **imaging/biopsy** should be sought **prior** to instituting antifungal therapy, but imaging would be the least invasive and most easily available modality of choice in order to investigate a suspected fungal infection.

**Neutropenic sepsis with no response to antibiotics at 48 hrs → possible fungal infection**

**Gram colony stimulating factor (G-CSF) can be used to boost neutrophil numbers in neutropenia**

**MRCPUK part 1exam: When is the risk of febrile neutropenia thought to be highest following chemotherapy? >> 10 days in to treatment**

## Eosinophilia

Causes of eosinophilia may be divided into pulmonary, infective and other.

### Pulmonary causes:

- Asthma
- Allergic Broncho pulmonary aspergillosis
- Churg-Strauss syndrome
- Loffler's syndrome
- Tropical pulmonary eosinophilia
- Eosinophilic pneumonia
- Hypereosinophilic syndrome

### Infective causes:

- Schistosomiasis
- Nematodes: **Toxocara**, Ascaris, Strongyloidiasis
- Cestodes: Echinococcus

### Other causes:

- **Drugs: sulfasalazine, nitrofurantoin**
- **Psoriasis**/eczema
- Eosinophilic leukemia (very rare)
- Cholesterol embolization
- Hodgkin's Lymphoma
- Addison's disease
- Eosinophilic Oesophagitis
- Eosinophilic Colitis.

Mnemonic: Causes of Eosinophilia is **NA ACCP**: **N**eoplasia, **A**ddison Disease, **A**sthma/**A**llergy, **C**ollagen Vascular disease, **C**holesterol emboli, **P**arasites.

### Eosinopenia (Decrease eosinophils)

#### Causes

- Cushing syndrome would result in a decrease in eosinophils.
- Corticosteroids can cause eosinopenia through sequestration of eosinophils in lymph nodes.

## Hyper-eosinophilic syndrome (HES)

### Definition

- **peripheral blood eosinophil count of >1.5 for more than 6 months.**
- In hypereosinophilic syndrome, the eosinophils represent more than **20** percent of the cell population in the bone marrow.
- HES are defined as the association of Hypereosinophilia (as defined above), with eosinophil-mediated organ damage, in which other causes for the damage have been excluded.

### Features

- Hypereosinophilic syndrome most commonly causes manifestations involving the **skin**.
- pruritus.
- fatigue, myalgia,
- fever, night sweats,
- diarrhoea
- The most common neurological manifestation of hypereosinophilic syndrome is **stroke**.
- Other symptoms depend on the organ involved:
  - cardiac disease causes chest pain and dyspnoea,
  - respiratory disease presents with a dry cough.

### Treatment

- The first line of treatment of patients with non-myeloid hypereosinophilic syndrome is **glucocorticoids**.
- The best initial therapy for patients with hypereosinophilic syndrome associated with Fip1-like1-platelet-derived growth factor receptor alpha mutation is **imatinib.**

# Lymphopenia

## Causes

- common finding in elderly patients.
  - If greater than 0.5 * $10^9$/l no action is normally needed
- immunosuppressive drugs e.g. methotrexate
- viral infections e.g. HIV
- non-viral infections e.g. tuberculosis, malaria
- autoimmune disorders e.g. rheumatoid
- lymphoproliferative disorders

# Thrombocytosis

Thrombocytosis is an abnormally high platelet count, usually > 400 * $10^9$/l.

**Thrombopoietin** is the key hormone in the regulation of megakaryocyte differentiation.

The most common cause of thrombocytosis is a **reactive thrombocytosis**.

## Causes of thrombocytosis:

- Reactive: platelets are an acute phase reactant - platelet count can increase in response to stress such as an exercise, severe infection or surgery.
- **Essential** thrombocytosis, or as part of **another myeloproliferative** disorder such as chronic myeloid leukaemia (CML) or polycythaemia rubra Vera (PRV).
- **Malignancy**.
- **Hypersplenism**.

## Essential thrombocytosis (ET):

Essential thrombocytosis is one of the **myeloproliferative** disorders which overlaps with CML, PRV and Myelofibrosis.

Megakaryocyte proliferation results in an overproduction of platelets.

In essential thrombocytosis low risk patients have a risk of thrombosis similar to that of the age and sex-matched population and a very low risk of life-threatening bleeding, supporting close observation as the most sensible approach.

Generally, the prognosis is extremely **good** in ET with survival of over two decades expected.

### Features:

- Platelet count > 600 * $10^9$/l.
- Both **thrombosis** (venous or arterial) and **haemorrhage** can be seen.
- A characteristic symptom is a **burning sensation in the hands.**
- A **JAK2 kinase (V617F mutation)** is found in around **50%** of patients.

**There are a number of adverse prognostic markers for (ET):**

- **Age above 60**
- **Symptomatology** - particularly **thrombosis** and
- **Platelet count above 1500.**

### Management:

- **Hydroxyurea (Hydroxycarbamide 500 mg Capsule)** is widely used to reduce the platelet count.
- Low-dose aspirin may be used to reduce the thrombotic risk.
- Interferon-α is also used in younger patients.
- Anagrelide is a second line drug in ET and has been associated with increased bone marrow fibrosis.

**EX:** A 60-year-old female presents with a platelet count of **768** ×109/L (150 - 400). On examination she has **isolated mild splenomegaly >>> myeloproliferative disorder >>>> Bone marrow biopsy with molecular studies >>> Treatment: ASA+ Hydroxyurea.**

## Thrombocytopenia

### Causes of severe thrombocytopenia:

- **ITP**
- **TTP**
- **DIC**
- **Hematological malignancy**

### Causes of moderate thrombocytopenia:

- **HIT** (Heparin induced thrombocytopenia).
- **Drug**-induced (e.g. quinine, diuretics, sulphonamides, aspirin, thiazides)
- **Alcohol**
- Vit. B12 deficiency
- **Liver** disease
- Hypersplenism
- Viral infection (EBV, HIV, hepatitis)
- **Pregnancy**
- **SLE/Antiphospholipid syndrome**

### Drug-induced thrombocytopenia (probable immune mediated):

- **Heparin**
- **NSAIDS**
- **Quinine**
- **Abciximab**
- **Diuretics**: furosemide, thiazides
- **Antibiotics: Penicillins, Sulphonamides, Rifampicin**
- **Anticonvulsants: Carbamazepine, Valproate**

## Idiopathic thrombocytopenic purpura (ITP)

- ITP is an immune mediated reduction in the platelet count.
- Antibodies are directed against **the glycoprotein IIb-IIIa** or Ib-V-IX complex.
- Common cause of death is **bleeding** (mainly **intracranial**).
- Over recent years a **familial propensity** for the development of ITP has been identified, although the particular gene susceptibility is yet to be identified.
- ITP can be divided into acute and chronic forms:

### Acute ITP:

- More commonly seen in children
- Equal sex incidence
- May follow an infection or vaccination
- Usually runs a self-limiting course over 1-2 weeks

### Chronic ITP:

- More common in young/middle-aged women
- Tends to run a relapsing-remitting course

### Evan's syndrome:

- **ITP in association with autoimmune hemolytic anaemia (AIHA).**

### Investigations:

- **Antiplatelet autoantibodies (usually IgG).**
- **Blood film shows occasional giant platelets**: The bone marrow is still working as there are **giant platelets seen on film**, which you see when there is peripheral consumption of the platelets.
- **Bone marrow aspiration** shows ↑ megakaryocytes in the marrow, this should be carried out prior to the commencement of steroids in order to **rule out** leukaemia.

In ITP >>> The most important investigation is a **blood film**, although not diagnostic, this will confirm the CBC findings and also exclude more sinister pathology such as leukemia.

**Management:**

- **Oral prednisolone (80% of patients respond): prednisolone 60 mg daily.**
- **IVIG immunoglobulins.**
- Immunosuppressive drugs e.g., cyclophosphamide.
- Splenectomy if platelets < 30 after 3 months of steroid therapy.
- Platelet stimulating factors are under development; these are expected to play role in future management.

Isolated thrombocytopenia in a well patient >>> points to a diagnosis of ITP.

## The management of ITP post-splenectomy:

- **Exclusion** of accessory splenic tissue by imaging studies
- **Confirming** post-splenectomy changes (Howell-Jolly bodies and target cells) on blood film examination.
- **Thrombopoietin** agonists (eltrombopag or romiplostim).
- **Immunosuppressant** agents like: Cyclosporine, MMF and Rituximab.

**NB:** The management of (**ITP**) which presents with a **catastrophic bleed** is aimed at achieving a **rapid rise in platelet count** to reduce the morbidity >>> **Methylprednisolone pulse IV + IVIG and platelet transfusion.**
Although platelet transfusions are not efficacious in ITP (due to transfused platelets being consumed in the same way as platelets released from bone marrow), they are useful in this setting, together with high doses of intravenous steroids and immunoglobulins.
**EX**: Male pt. 33 years old with ITP (PLT 3), he is commenced on prednisone 1 mg/kg/day. On the 3rd day of his admission, he is noted to be hemiparetic. Urgent CT scanning of the brain shows a massive intracerebral haemorrhage with no midline shift >>> **Treatment: Methylprednisolone pulse IV + IVIG** and **platelet transfusion**, together with **consideration for urgent craniotomy** and intracranial clot evacuation by neurosurgeons.

## Remember the pseudo-thrombocytopenia:

**EDTA added to the CBC samples causes:**
**clumping of platelets,large clumps are interprited in automatic counters as one platelet so the total number is falsely reduced, clumps do occur duo to naturally occurring autoantibodies**
SO, the first step when new low platelet count develop is to request manual count and blood film or put the CBC sample in citrated tube.

# Thrombotic thrombocytopenic purpura (TTP)

**TTP** is life-threatening multi-system disorder characterized by **pentad.**
**TTP** is a **clinical diagnosis** and potential diagnosis in any patient with anemia and thrombocytopenia - **95%** of cases are **fatal if** left untreated.
Symptoms are usually non-specific.
High index of suspicion is necessary to make the diagnosis.
Renal and neurological dysfunctions are the main complications.
The survival rate has improved from about 3% prior to the 1960s to 85% now.

## Pathogenesis:

- Abnormally large and sticky multimers of **von Willebrand's factor** cause platelets to clump within vessels.
- In TTP there is a **deficiency of ADAMTS13** (a metalloprotease enzyme) which breakdowns large multimers of von Willebrand's factor.
- **Overlaps** with hemolytic uremic syndrome **(HUS). (See nephrology)**

## Features: (Typically **adult females**): Pentad (5):

- **Microangiopathic hemolytic anemia (MAHA):** by peripheral smear fragmented RBCs (schistocytes).
- **Thrombocytopenia with purpura.**
- **Neurological** abnormalities (microemboli in microcirculation): (usually more marked in TTP than in HUS). Neurological manifestations are present in most patients, and range from confusion and severe headache, to focal neurological abnormalities, seizures and coma.
- **Renal failure** (usually less marked in TTP than in HUS).
- **Fever**

**Not all of the above (pentad) may be present.**

**In practice, the triad** of **schistocytes, thrombocytopenia** and ↑ **LDH** are sufficient to make the diagnosis.

**Low platelets PLUS Neuro** signs and **purpura** >>> point towards TTP/HUS

## As an aide-memoire, this can be remembered as (TTP- PENTAD):

**P** - Pyrexia
**E** - Endothelial damage
**N** - Neurological abnormality
**T** - Thrombocytopenia
**A** - Anaemia (MAHA)
**D** - Damage to kidney.

## Other features are:

- Purpura, ecchymosis, and menorrhagia due to thrombocytopenia may also be seen in 20% of cases.
- Peripheral digit ischemic syndrome.
- Non-occlusive mesenteric ischemia.
- Adult respiratory distress syndrome (ARDS).

Livedo reticularis is not commonly seen in TTP. It occurs more commonly in conditions such as antiphospholipid syndrome and cholesterol embolism

## Additional laboratory findings:

- The **reticulocyte** count is generally elevated.
- **LDH** and **bilirubin** are often elevated as markers of hemolysis.
- **Direct Coombs' test** should be **negative** to **rule out** AIHA.
- **Normal clotting factors (PT & PTT)** should be **normal** to **rule out DIC.**
- Assays have been developed to measure **von Willebrand factor cleaving enzyme (ADAMTS-13) activity.** ADAMTS-13 activity can be **low**, and inhibitors to its activity can often be demonstrated in patients with TTP.

## Causes:

- Post-infection e.g. urinary, gastrointestinal
- Post BMT in AML.
- Malignant hypertension
- **Pregnancy**
- **Eclampsia, post-partum acute renal failure.**
- Drugs: cyclosporine, **OCP**, penicillin, **clopidogrel (Plavix),** acyclovir.
- Tumors (adenocarcinoma).
- SLE, Vasculitis, collagen vascular disease (scleroderma), cryoglobulinemia.
- HIV.

## NB: Causes of MAHA include:

- Thrombotic thrombocytopenic purpura (**TTP**)
- Haemolytic uraemic syndrome (**HUS**)
- Disseminated intravascular coagulation (**DIC**)
- Haemolysis by **prosthetic** heart valves
- **Malignant hypertension**
- **Pre-eclampsia**
- **HELLP** - haemolysis elevated liver enzymes and low platelets.
- **Septicaemia**
- **Vasculitis**

- **Connective** tissue disease (polyarteritis nodosa [**PAN**], **Wegener's**, systemic lupus erythematosus [**SLE**]).

**NB: The differential diagnosis is a pregnancy associated thrombotic microangiopathy, which includes:**

- Thrombotic thrombocytopenia purpura (TTP)
- Haemolytic uraemic syndrome (HUS)
- Disseminated Intravascular coagulation (DIC)
- Pre-eclampsia
- HELLP
- Acute fatty liver of pregnancy
- Systemic lupus erythematosus (SLE).

## Management:

- **Urgent Plasmapharesis:** Plasma exchange with **FFP (not Albumin)** (to replace the missing factor in TTP, called ADAMTS-13) is the ttt of choice.
- Steroids, Immunosuppressants: Vincristine
- Rituximab can be used.
- **No antibiotics** - may worsen outcome.
- Platelets transfusion is **contraindicated** in TTP as it has negative impact on prognosis unless mandatory indicated if with hemorrhage. The pathological basis relates to micro-thrombi formation which results in ischemia in affected blood vessels with ensuing end-organ damage (neurological, renal and cardiac).

**TTP >>> urgent plasma exchange with FFP** is first-line tratment

**TTP in pregnancy** typically occurs **early in pregnancy** - usually less than 24 weeks, whereas HELLP and pre-eclampsia occur usually much later.

The only management option for **TTP in pregnancy is plasma exchange. Delivery** has **no** effect on disease.

**NB: Tranexamic acid** is sometimes misused for bleeding in TTP, but it is **prothrombotic** and may be **worsening** the condition, hence it should be **stopped** in TTP.

**NB: TTP** can occur in **less than 1%** of patients receiving **clopidogril** or ticlopidine **>>> peripheral blood film >>> fragmented RBCs.**

**EX:** Pt after **2 weeks** from PCI and Plavix usage, develop Rt. sided weakness, bleeding tendency, low platelets, anaemia, renal impairment, fever, Disturbed LOC with confusion **>>> TTP due to clopidogril.**

# Venous thromboembolism (VTE)

## General risk factors:

- Increased risk with advancing age
- Obesity
- Family history of VTE
- Pregnancy (especially **puerperium**)
- Immobility
- Hospitalization
- Anesthesia
- Central venous catheter: femoral >> subclavian

## Underlying conditions:

- Malignancy
- Thrombophilia: e.g. Activated protein C resistance, protein C and S deficiency
- Heart failure
- Antiphospholipid syndrome
- Bechet's syndrome (arterial and venous).
- Polycythemia rubra vera.
- Nephrotic syndrome.
- Sickle cell disease.
- Paroxysmal nocturnal hemoglobinuria (arterial and venous)
- Hyperviscosity syndrome.
- Homocystinuria (mainly arterial).

## Medication:

- Combined oral contraceptive pill: **3rd generation more** than 2nd generation.
- HRT Hormone replacement therapy.
- Raloxifene and Tamoxifen.
- **Antipsychotics** especially **Olanzapine (Zyprexa ®)** have recently been shown to be a risk factor.

**SIGN** also state that the following are risk factors for **recurrent VTE:**

- Previous unprovoked VTE (50% found to have clear cause )
- **Male sex.**
- Obesity.
- Thrombophilia's.

Deep vein thrombosis (DVT): diagnosis and management(pleases refer to NICE guidelines.March 2020)

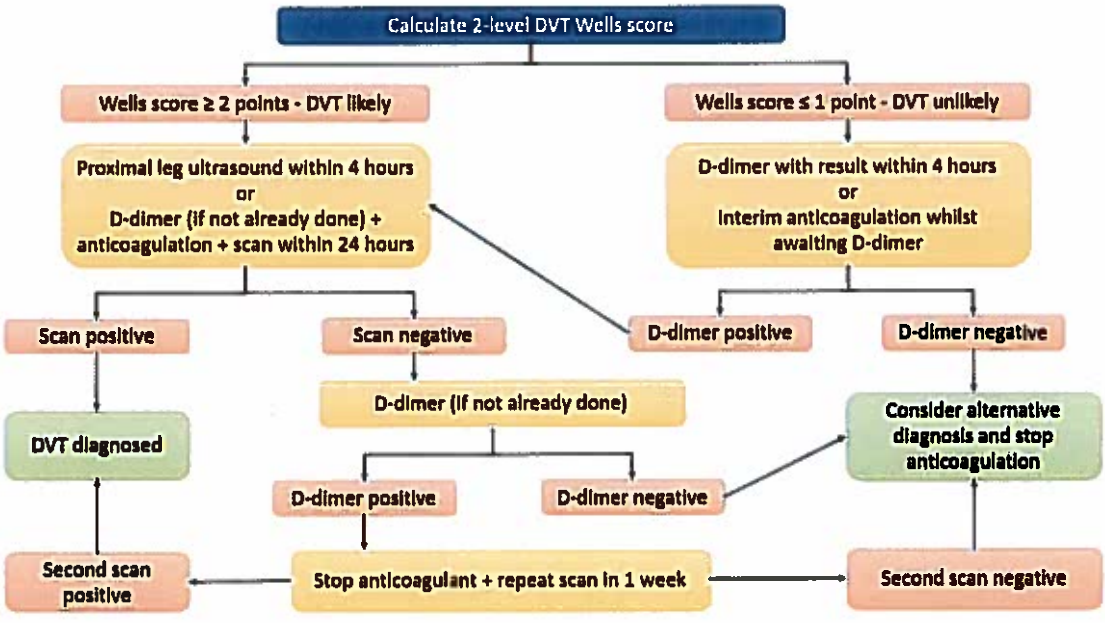
## Diagnosis:

NICE guidelines 2020 relating to the investigation and management of DVT.

If a patient is suspected of having a DVT a two-level DVT **Wells score** should be performed:

### Two-level DVT Wells score

| Clinical feature | Points |
|---|---|
| Active cancer (treatment ongoing, within 6 months, or palliative) | 1 |
| Paralysis, paresis or recent plaster immobilization of the lower extremities | 1 |
| Recently bedridden for 3 days or more or major surgery within 12 weeks requiring general or regional anesthesia | 1 |
| Localized tenderness along the distribution of the deep venous system | 1 |
| Entire leg swollen | 1 |
| Calf swelling at least 3 cm larger than asymptomatic side | 1 |
| Pitting oedema confined to the symptomatic leg | 1 |
| Collateral superficial veins (non-varicose) | 1 |
| Previously documented DVT | 1 |
| An alternative diagnosis is at least as likely as DVT | 2 |


Calculate 2-level DVT Wells score
Wells score ≥ 2 points - DVT likely
Wells score ≤ 1 point - DVT unlikely
Proximal leg ultrasound within 4 hours or D-dimer (if not already done) + anticoagulation + scan within 24 hours
D-dimer with result within 4 hours or Interim anticoagulation whilst awaiting D-dimer
Scan positive
Scan negative
D-dimer positive
D-dimer negative
DVT diagnosed
D-dimer (if not already done)
Consider alternative diagnosis and stop anticoagulation
D-dimer positive
D-dimer negative
Second scan positive
Stop anticoagulant + repeat scan in 1 week
Second scan negative

### Clinical probability simplified score:

- DVT likely: 2 points or more
- DVT unlikely: 1 point or less

### If a DVT is 'likely' (2 points or more):

- A proximal leg vein ultrasound scan should be carried out within 4 hours and, if the result is negative, a D-dimer test.
- If a proximal leg vein ultrasound scan cannot be carried out within 4 hours a D-dimer test should be performed and low-molecular weight heparin administered whilst waiting for the proximal leg vein ultrasound scan (which should be performed within 24 hours).

### Start Interim therapeutic anticoagulation for suspected DVT or PE.

- Follow the recommendations on when to offer interim therapeutic anticoagulation for suspected proximal DVT or PE in the section on diagnosis and initial management. [2020] If possible, choose an interim anticoagulant that can be continued if DVT or PE is confirmed (see the section on anticoagulation treatment for confirmed DVT or PE). [2020] In March 2020, direct-acting anticoagulants and some low molecular weight heparins (LMWHs) were off label for the treatment of suspected DVT or PE. See NICE's information on prescribing medicines.When using interim therapeutic anticoagulation for suspected proximal DVT or PE:
- carry out baseline blood tests including full blood count, renal and hepatic function, prothrombin time (PT) and activated partial thromboplastin time (APTT) • do not wait for the results of baseline blood tests before starting anticoagulation treatment.
- review, and if necessary, act on, the results of baseline blood tests within 24 hours of starting interim therapeutic anticoagulation. [2020]

### If a DVT is 'unlikely' (1 point or less)

- Perform a D-dimer test and if it is positive arrange:
- A proximal leg vein ultrasound scan within 4 hours
- If a proximal leg vein ultrasound scan cannot be carried out within 4 hours low-molecular weight heparin should be administered whilst waiting for the proximal leg vein ultrasound scan (which should be performed within 24 hours).

### Signs or symptoms of PE:

For people who present with signs or symptoms of PE, such as chest pain, shortness of breath or coughing up blood, assess their general medical history, do a physical examination and offer a chest X-ray to exclude other causes.

**Pulmonary embolism rule-out criteria (the PERC rule):**

If clinical suspicion of PE is low (the clinician estimates the likelihood of PE to be less than 15% based on the overall clinical impression, and other diagnoses are feasible), consider using the pulmonary embolism rule-out criteria (PERC) to help determine whether any further investigations for PE are needed. Use the 2-level PE Wells score to estimate the clinical probability of PE.

**PE likely (Wells score more than 4 points):** For people with a likely PE Wells score (more than 4 points):

- **offer** a computed tomography pulmonary angiogram (CTPA) immediately if possible, or for people with an allergy to contrast media, severe renal impairment (estimated creatinine clearance less than 30 ml/min) or a high risk from irradiation, assess the suitability of a ventilation/perfusion single photon emission computed tomography (V/Q SPECT) scan or, if a V/Q SPECT scan is not available, a V/Q planar scan, as an alternative to CTPA. If a CTPA, V/Q SPECT or V/Q planar scan cannot be done immediately, offer interim therapeutic anticoagulation [2012, amended 2020].

**If PE is identified by CTPA, V/Q SPECT or V/Q planar scan:**

- offer or continue anticoagulation treatment.
- if anticoagulation treatment is contraindicated, consider a mechanical intervention. For people with PE and hemodynamic instability offer thrombolytic therapy. [2012, amended 2020]

**If PE is not identified by CTPA, V/Q SPECT or V/Q planar scan consider a proximal leg vein ultrasound scan.**

- If DVT is suspected follow VTE GUIDELINES.
- if DVT is not suspected: — stop interim therapeutic anticoagulation — think about alternative diagnoses — tell the person that it is not likely they have PE. Discuss with them the signs and symptoms of PE and when and where to seek further medical help.

**PE unlikely (Wells score 4 points or less):**

**Offer people with an unlikely PE Wells score (4 points or less):**

- a D-dimer test with the result available within 4 hours if possible or
- if the D-dimer test result cannot be obtained within 4 hours, offer interim therapeutic anticoagulation while awaiting the result (see the section on interim therapeutic anticoagulation for suspected DVT or PE).

**If the D-dimer test result is:**

- **positive,** follow the actions in recommendations ASSESS the risk and discuss with seniors and do CTPA or alternatives.
- **negative:** — stop interim therapeutic anticoagulation — think about alternative diagnoses • tell the person that it is not likely they have PE. Discuss with them the signs and symptoms of PE and when and where to seek further medical help.

**Anticoagulation treatment for confirmed DVT or PE**

- Offer anticoagulation treatment for at least 3 months to people with confirmed proximal DVT or PE. For recommendations on treatment after 3 months see the section on long-term anticoagulation for secondary prevention. [2020]
- If not already done, carry out baseline blood tests, as outlined in recommendation. when starting anticoagulation treatment. [2020]
- When offering anticoagulation treatment, take into account comorbidities, contraindications and the person's preferences.

**Follow the recommendations on anticoagulation treatment in the sections on:**

- DVT or PE in people at extremes of body weight.
- PE with hemodynamic instability.
- DVT or PE with renal impairment or established renal failure.
- DVT or PE with active cancer.
- DVT or PE with triple positive antiphospholipid syndrome. [2020].

Offer either apixaban or rivaroxaban to people with confirmed proximal DVT or PE (but see recommendations for precautions).

If neither apixaban nor rivaroxaban is suitable offer:

- LMWH for at least 5 days followed by dabigatran or edoxaban
  **or**
- LMWH concurrently with a vitamin K antagonist (VKA) for at least 5 days, or until the INR is at least 2.0 in 2 consecutive readings, followed by a VKA on its own. **Do not routinely offer unfractionated heparin (UFH) with a VKA to treat confirmed proximal DVT or PE unless the person has renal impairment or established renal failure,or an increased risk of bleeding.**

Do not routinely offer self-management or self-monitoring of INR to people who have had DVT or PE and are having treatment with a VKA.

- Anticoagulation should be continued for **at least 3 months**. At 3 months, NICE advise that clinicians should 'assess the risks and benefits of extending treatment'

- NICE add 'consider extending warfarin **beyond 3 months** for patients with ***unprovoked*** **proximal DVT** if their risk of VTE recurrence is high and there is no additional risk of major bleeding'. This essentially means that if there was no obvious cause or provoking factor (surgery, trauma, significant immobility) it may imply the patient has a tendency to thrombosis and should be given treatment longer than the norm of 3 months. In practice most clinicians give **6 months** of anticoagulation for patients with an unprovoked DVT/PE.
- For patients with a **second time provoked DVT** (e.g., also post-operative DVT for 2nd time) >>> anticoagulation for **6 months** and search for inherited thrombophilia (n.b:50% of unprovoked cases found to have inherited thrombophilia).
- For patients with **recurrent DVT whilst on** anticoagulation is an indication for **life-long** anticoagulation.
- For patients with **active cancer + VTE >>>** NICE recommend using **LMWH for 6 months.** (LMWH has the advantage of being easier to reverse and stop if a cancer-related bleed occurs, for example massive hemoptysis in a patient with lung cancer).

**N.B:** Warfarin does not undergo extensive hepatic first-pass metabolism.

**Venous thromboembolisms - length of warfarin treatment**
- Provoked (e.g., recent surgery): 3 months
- Unprovoked: 6 months

## Further investigations and thrombophilia screening:

As both **malignancy** and **thrombophilia** are obvious risk factors for deep vein thrombosis NICE make recommendations on how to investigate patients with unprovoked clots.

Offer all patients diagnosed with **unprovoked DVT or PE** who are not already known to have cancer the **following investigations for cancer:**

- A physical examination (guided by the patient's full history) and
- A chest X-ray and
- Blood tests (CBC, serum calcium and LFTs) and urinalysis.
- Consider further investigations for cancer with an **abdominal-pelvic CT scan** (and a **mammogram** for women) in **all** patients **aged over 40** years **with a first unprovoked DVT or PE.**

## Thrombophilia screening:

- Not offered if patients will be on lifelong warfarin (i.e. won't alter management)
- Consider testing for **Antiphospholipid antibodies** if unprovoked DVT or PE

- Consider testing for **hereditary thrombophilia** in patients who have had unprovoked DVT or PE and who have a first-degree relative who has had DVT or PE.

## Pregnancy: DVT/PE

### Overview:

- Pregnancy is a hypercoagulable state
- Majority occurs in **last trimester**

### Pathophysiology:

- Increase in factors VII, VIII, X and fibrinogen
- **Decrease in protein S**
- Uterus presses on IVC causing venous stasis in legs

### Management:

- Warfarin contraindicated
- S/C LMWH preferred to IV heparin (less bleeding and thrombocytopenia).

## Superficial thrombophlebitis

- Superficial thrombophlebitis, as the name suggests describes the inflammation associated with thrombosis of one of the superficial veins, usually the long saphenous vein of the leg.
- This process is usually non-infective in nature but secondary bacterial infection may rarely occur resulting in septic thrombophlebitis.
- Around 20% with superficial thrombophlebitis will have an underlying deep vein thrombosis (DVT) at presentation and 3-4% of patients will progress to a DVT if untreated.
- The risk of DVT is partly linked to the length of vein affected - an inflammed vein > 5 cm is more likely to have an associated DVT.

### Management

- Traditionally NSAIDs have been used, with topical NSAIDs for limited and mild disease and oral NSAIDs for more severe disease.
- Topical heparinoids have also be used in the management of superficial thrombophlebitis.
- A Cochrane review however found topical NSAIDs and heparinoids have no significant benefit in terms of reducing extension or progression to DVT.
- Oral NSAIDs were however shown to reduce the risk of extension by 67%.

- Compression stockings are also used.
- Remember that the ankle-brachial pressure index (ABPI) should be measured before prescribing compression stockings, particularly if using class 2 or above stockings.
- One of the major changes to the management of superficial thrombophlebitis is the increased use of low-molecular weight heparin. This has been shown to reduce extension and transformation to DVT.
- **SIGN produced guidelines in 2010:**
  - Patients with clinical signs of superficial thrombophlebitis affecting the proximal long saphenous vein should have an ultrasound scan to exclude concurrent DVT.
  - Patients with superficial thrombophlebitis should have anti-embolism stockings and can be considered for treatment with prophylactic doses of LMWH for up to 30 days or fondaparinux for 45 days.
  - If LMWH is contraindicated, 8-12 days of oral NSAIDS should be offered.
  - Patients with superficial thrombophlebitis at, or extending towards, the sapheno-femoral junction can be considered for therapeutic anticoagulation for 6-12 weeks.
- This may be a significant departure from our current practice - the majority of patients with superficial thrombophlebitis (i.e. those affecting the long saphenous vein) should be referred for an ultrasound scan.

## Hepatic Veno-Occlusive Disease (VOD) = Sinusoidal obstruction syndrome

It is a complication of high dose chemotherapy given before a bone marrow transplant (BMT).
The name Sinusoidal obstruction syndrome is preferable if VOD happens as a result of chemotherapy or BMT.
It is usually occurs within 2 weeks of BMT.

**Features:** **weight gain, fluid retention, ascites, impending pulmonary oedema, pleural effusion, hepatomegaly, Jaundice** with **elevated liver enzymes**, complicated by MOF.
**Diagnosis:** Abd U/S, Liver biopsy shows centrilobular necrosis.
**Treatment**: Supportive: fluid balance, heparin & tPA.

## Leuco-erythroblastic anaemia

**leuco-erythroblastic anaemia (left-shifted granulocytic series and nucleated red blood cells)**

### This can be seen with:

- high bone marrow turnover, e.g. in severe haemolytic anaemia
  - (the reticulocyte count will be high),
- myelofibrosis and chronic myeloid leukaemia
  - (where there will be splenomegaly and the white cell and platelet count will usually be raised)
- bone marrow invasion.
  - **Often in bone marrow invasion the invading malignancy will already have been diagnosed previously.**
  - The diagnosis requires a bone marrow trephine, which will usually show replacement of haematopoietic tissue with malignant cells.

## Drug-induced pancytopenia

### Drug causes of pancytopaenia

- Cytotoxics
- Antibiotics: **Trimethoprim**, Chloramphenicol
- Anti-rheumatoid: Gold, Penicillamine
- **Carbimazole** (It causes both agranulocytosis and pancytopaenia)
- Anti-epileptics: **Carbamazepine**
- **Sulphonylureas**: tolbutamide

*causes both agranulocytosis and pancytopaenia

## Coagulation study

### Prothrombin time (PT)

- Prothrombin time (PT) is a measure of the time it takes for the extrinsic pathway to create a fibrin clot.
- tests function of factors (I, II, V, **VII**, X)
  - defect in any of these → ↑ PT
  - e.g. vitamin K deficiency
- **best test to follow warfarin therapy**
  - normalized as an INR (international normalized ratio)
  - note also increases PTT time

- also used to measure hepatic function as most of the factors are synthesized in the liver Used to monitor the extrinsic pathway
- Factors make up the extrinsic pathway:
  - Damaged endothelium → tissue factor release → Factor VII activation → common pathway activation
- In patients with vitamin K deficiency, the PT is typically prolonged while the partial thromboplastin time (PTT) is usually normal.
- Long-term use of antibiotics >> changes in the gut flora >> vitamin K deficiency >> ↑PT
  - Long-term use of antibiotics (particularly cephalosporins like cefepime) would cause changes in the gut flora that result in vitamin K deficiency (due to decreased populations of the bacteria that synthesize it).
  - vitamin K deficiency would impair the gamma-carboxylation of factors II, VII, IX, and proteins C and S.
  - As a result, the **PT**, which **measures the clotting time of the extrinsic pathway** (starting with tissue factor and factor VII), would **increase**, just as it would in a patient on warfarin.

**Partial Thromboplastin Time (PTT)** (sometimes also called Activated Partial Thromboplastin Time)

- tests function of all factors EXCEPT (VII, XIII)
  - defect in any of these→ ↑ PTT
- when prolonged indicating hemophilia or (sometimes) von Willebrand's Disease.
- **best test to follow heparin therapy**
  - note also increases PT time
- Used to monitor the **intrinsic pathway**
- Factors make up the intrinsic pathway:
  - Factors XII, XI, IX, VIII.
- **elevated APTT could be due to:**
  - treatment with heparin
  - haemophilia
  - von Willebrand's disease, or
  - antiphospholipid syndrome.

**The commonest cause of reduced APTT is >> in-vitro clotting cascade activation, but tests should be repeated to exclude pathological causes of hypercoagulability.**

**DIC vs TTP**

- DIC is distinguished from thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS) based on coagulation studies.

- Although TTP and HUS are also microangiopathic hemolytic anemias, patients with these conditions do not have derangement or consumption of clotting factors.
  - **DIC >> Increased PT, PTT, decreased platelets**
  - TTP & HUS >> normal PT, normal PTT, and **decreased platelets.**

**Isolated factor deficiency**

- Normal PT, **increased PTT**, and normal platelets suggests an isolated factor deficiency such as hemophilia A and B, in which there is a deficiency of factors VIII and IX, respectively.
- An isolated elevated PTT may also suggest von Willebrand's disease.

| Disease | PT | PTT | Platelet count | Bleeding time |
|---|---|---|---|---|
| Warfarin (or vitamin K deficiency) | Raised | Raised (in severe or prolonged cases)/nl | Raised | nl |
| DIC | Raised | Raised | Decreased | Raised |
| Thrombocytopenia | nl | nl | Decreased | Raised |
| Bernard-Soulier | nl | nl | Decreased | Raised |
| Hemophilia (A or B) | nl | Raised | nl | nl |
| von Willebrand | nl | nl / raised | nl | Raised |
| Glanzmann's | nl | nl | nl | Raised |

**Giant platelet syndrome (Bernard-Soulier syndrome; BSS)**

- is a defect in platelet adhesion.
- The genetic defect is in glycoprotein 1b (GP1b).
- characterized by increased megakaryocytes and abnormally large platelets on peripheral smear, hence its name.
- **thrombocytopenia and an elevated bleeding time but a normal prothrombin time (PT) and partial thromboplastin time (PTT).**
- BSS can be distinguished from a deficiency in von Willebrand factor (vWF) by a **ristocetin test**.
  - Ristocetin is an antibiotic that causes vWF to bind to GP1b, causing agglutination in normal blood.
  - In patients with either defective vWF or GP1b (BSS), platelets do not aggregate in the presence of ristocetin.
  - The addition of normal plasma corrects this defect in von Willebrand's disease, but not in BSS (because the platelet receptor remains defective).

# Myelodysplasia (Myelodysplastic syndrome (MDS)

It occurs mainly in **elderly** about **70-80** years old.

**Transformation into AML occurs in around 30% of patients.**

Presentation: due to **pancytopenia**: Anaemia, Infection and Bleeding

**Median survival is 2 years.**

Patients are more likely to have **serious infections** or **life-threatening bleeds** than blastic transformation.

Few patients require aggressive therapy and most need **only supportive care**. As the vast majority are elderly patients with other medical conditions, excessive intervention is unwarranted.

Old patient with lethargy and pancytopenia >>> Myelodysplasia

## Investigations:

- CBC: bone marrow failure, **small blasts**
- Bone marrow: ↑ cellularity, **ring sideroblasts**.

The disease can be classified into the following subtypes (WHO) 2008:

1) Refractory anaemia with unilineage dysplasia- i.e. anaemia, neutropenia or thrombocytopenia (<5% blasts).
2) Refractory anaemia with ring sideroblasts (<5% blasts; >15% sideroblasts
3) Refractory anemia with multilineage dysplasia (based on bone marrow dysplasia in 2 or more myeloid lineages).
4) Refractory anaemia with excess blasts-1(5-9% blasts) and refractory anemia with excess blasts -2 (10-19%).
5) Myelodysplasia unclassified.
6) Myelodysplasia with isolated 5qdel (cytogenetic abnormality with prognostic significance).

If much Blasts > 20% is now classified as acute myeloid leukemia (**AML**).

## Managements:

- < 5% blasts in bone marrow → conservative
- ↑ TLC → "Gentle" chemotherapy
- < 60 years old → "Intensive" chemotherapy
- Anaemia: PRBCs transfusion + iron chelation with Desferrioxamine SC.

## Laboratory findings in haematological disease

The table below shows some very selective laboratory findings that are commonly tested in the exam:

| Test | Interpretation |
|---|---|
| **Haptoglobin**<br>(Remember haptoglobin binds to free haemoglobin) | **Decrease**<br>intravascular haemolysis |
| **MCHC** | **Increased**<br>• hereditary spherocytosis<br>• autoimmune haemolytic anemia*<br>**Decreased**<br>• microcytic anaemia (e.g. iron deficiency) |

*associated with spherocytosis

## Thrombophilia: causes

**Inherited:**

- Protein C deficiency
- Protein S deficiency
- Antithrombin III deficiency
- **Factor V Leiden mutation (FVL) (Activated protein C resistance):**

The **most common** Antiphospholipid syndrome

- The OCP
- PNH (paroxysmal nocturnal haemoglobinuria).
- PRV (polycythaemia rubra vera).

**Thrombophilia testing is considered useful in patients presenting with:**

- A first episode of venous thromboembolism (VTE) at a **young age** (usually considered **less** than **45** years of age).
- **Idiopathic** venous thrombosis (so no need if the patient clearly has a provoked DVT relating to a fracture).
- A **family history** of thrombosis, particularly in a **first** degree relative.
- VTE in an **unusual** vascular territory.
- **Neonatal purpura fulminans.**
- **Warfarin** induced **skin necrosis (WISN).**

# Protein C deficiency

Protein C deficiency is an autosomal codominant condition which causes an increased risk of thrombosis.

## Features:

- Venous thromboembolism
- **Skin necrosis** following the commencement of **warfarin (Warfarin induced skin necrosis) (WISN)**: when warfarin is first started biosynthesis of protein C is reduced. This results in a temporary paradoxical procoagulant state after initially starting warfarin, normally avoided by concurrent heparin administration. Thrombosis may occur in venules **(microthrombi)** in the skin particularly in the **adipose** areas such as buttocks and breast (**skin necrosis**).

## Treatment:

- Supportive by Vit K, FFP to replace protein C level.
- Prostacyclin and protein C infusion has been trialed.
- Warfarin can be reintroduced at a lower loading dose, but recurrence can occur.

**NB**: Heparin induced skin necrosis can be indistinguishable from WISN, but is antibody mediated, and occurs in **5-10 days after** commencing heparin, usually with the presence of **heparin/platelet factor 4 antibodies**.

Protein C is an inhibitor that, once activated, inhibits clot formation and enhances fibrinolysis. It is liver synthesised and vitamin K dependent. Protein C is converted to an active enzyme by a thrombin-thrombomodulin complex on the endothelial cell surface.

Activated protein C inhibits a plasminogen activator inhibitor, which results in enhanced fibrinolysis, and, with protein S as a co-factor, inhibits the clotting of the activated factors 5 and 8 by limited proteolysis. Activated protein C thus controls the conversion of factor 10 to 10a and prothrombin to thrombin.

**EX**: Pt with DVT and has started enoxaparin 1 mg/kg BID and warfarin 10 mg >>> on the **2nd day**, there is **black lesions** over the **buttocks** with **normal platelet count** >>> **WISN**, the most likely diagnosis is **protein C deficiency**.

# Activated protein C resistance (Factor V Leiden mutation) (FVL)

Activated protein C resistance is **the most common inherited thrombophilia.**

It is due to a mutation in the Factor V Leiden gene.

It is caused by an amino acid substitution that impairs the ability of activated protein C and S to inactivate factor Va.

It is mostly inherited in an **autosomal dominant** fashion and is present in **5-9%** of the **European** population but is rare in people of Asian and African descent.

About **5%** of the **UK** population carry a factor 5 Leiden mutation.

Heterozygotes have a 5-fold risk of venous thrombosis whilst **homozygotes** have a **50**-fold increased risk.

Cascade screening of adult family members is appropriate and members who carry FVL can receive lifestyle counselling regarding contraception and long journeys.

Women who take the OCP however have a significantly raised risk of venous thrombosis and currently the use of any type of OCP in women with confirmed factor 5 Leiden mutation is not recommended.
**General population screening is not practical or cost-effective** at present, but **screening of patients with relatives known** to be affected is recommended, if a mutation is **found** then **stop OCP** and **non-hormonal contraception** should be recommended unless a woman has completed her family and expresses a preference for **sterilization**.

Factor V Leiden mutation results in >> activated **protein C resistance**
Any white patient < 45 years old with thrombotic event, should make you think of factor V Leiden mutation.

**EX:** Female 30 years old on OCP with 1st time acute DVT and thrombophilia screen revealed that she has factor V Leiden mutation >>> **Warfarin for 6 months (NOT lifelong).**
Recent population analysis / case series have now suggested that **the risk benefit for lifelong warfarin** in a patient with factor V Leiden mutation who has a **first DVT** may not be positive due to bleeding risk, as such lifelong warfarin is **no longer recommended** in this situation for a **first** event.

**NB: Activated protein C resistance (Factor V Leiden)** >> is the most common inherited **thrombophilia.**
**Von Willebrand's disease**>>is the most common inherited **bleeding** disorder.

## Haemophilia

Hemophilia is an **X-linked recessive** disorder of coagulation.
Up to 30% of patients have no family history of the condition.

| | |
|---|---|
| Haemophilia **A** | **X-linked** genetic disorder due to deficiency of factor **VIII (8)** and represents **90%** of Haemophilia cases. |
| Haemophilia **B** (Christmas disease) | **X-linked** genetic disorder due to deficiency of factor **IX (9).** It is **more severe** but **less common** than Haemophilia A, it represent about **20%** of Haemophilia cases. . |
| Haemophilia **C** | **Autosomal recessive** genetic **(NOT X-Linked),** due to deficiency of factor **XI (11).** It is not completely recessive so heterozygous individuals also shows ↑ bleeding. |

### Features:

- **Hemoarthroses**, hematomas
- Prolonged bleeding after surgery or trauma

### Blood tests:

- **Prolonged APTT**
- With **NORMAL** bleeding time, thrombin time and prothrombin time.

Up to 10-15% of cases with haemophilia A develop antibodies to factor VIII treatment

**NB**: **Prolonged APTT** may be caused by (4):
**- Heparin therapy,**
**- Von Willebrand's disease (vWD)**, or
**- Haemophilia A or B or acquired factor 8 VIII deficiency,**
**- Antiphospholipid syndrome.**

Haemophilia is an X-linked recessive disorder and would hence be expected **only** to occur in **males**. With exception that only appears in **female** patient if with **Turner's** syndrome **only have one X chromosome** however, they may develop X-linked recessive conditions.

**EX:** A 45-year-old man is to undergo knee surgery. He has a history of **factor IX deficiency**. You are concerned about the prospect of significant bleeding during surgery.

What is most likely to reduce his risk of bleeding >> **Tranexamic acid.**

**Tranexamic acid competitively** inhibits activation of plasminogen, thereby **reducing the conversion of plasminogen to plasmin.**

This results in slower degradation of fibrin clots, fibrinogen and other plasma proteins including factors V and VIII.

As such it may be of value in **patients undergoing surgery** who have inherited **factor IX deficiency** in order to reduce the perioperative risk of bleeding.

**Recombinant factor IX** is of course also an option where it is available, although patients have a high tendency to form neutralising antibodies to factor IX.

**NB: Vasopressin (Desmopressin)** is associated with a significant increase in levels of both factor VIII and von Willebrand factor in haemophilia A. Any increase seen in factor IX levels after vasopressin is however much more minor. As such tranexamic acid is a much more useful therapeutic choice.

## Acquired Haemophilia

It is associated with **anti-factor VIII IgG antibodies** and is **idiopathic** in the majority of cases.

### Association:

- Autoimmune disease: RA or IBD
- Drugs: Phenytoin

### Management:

- Factor **VIII** replacement.
- Immunosuppressive: steroids ± steroid sparing agents as cyclosporine.

**EX:** Male patient 65 years old with spontaneous haematoma in his right thigh, with past medical history of RA, Labs are normal apart from mild prolonged PTT >>> **acquired haemophilia.**
**Haemophilia A or B or VWD would not present de-novo at the age of 65.**

## Factor VII (7) Deficiency

It is **very rare**, it is inherited as an autosomal recessive fashion, and tends to cause **mild to moderate** bleeding disorder.

**Factor 7** is the only factor unique to the **PT** (prothrombin time).

**Factor 7** deficiency >>> **prolonged PT** with **normal PTT**.

**TREATMENT**: factor replacement with FFP or recombinant activated factor VII.

## Acquired Factor VIII (8) Deficiency

It results from the development of **inhibitors** against factor **VIII** coagulation factor. It occurs mainly in **elderly** or during pregnancy, often in association with concurrent **autoimmune** disease or **malignancy**.

**Bleeding** can be **severe** to the point that great care should be taken with cannula insertion since compartment syndrome may ensure.

### Association:

- Malignancy
- Autoimmune disorders: Psoriasis & Pemphigus
- Drugs: penicillins, cephalosporins

### Diagnosis:

- Bleeding tendency.
- **Prolonged PTT** (Intrinsic pathway).
- PTT doesn't correct/will only correct **slightly** with adding of **FFP**.
- **Factor VIII inhibitor** is detected.
- Bethesda titre can quantify the inhibitor.
- There is 20% mortality rate.

### Treatment:

- Recombinant Factor VIII replacement is usually ineffective as the inhibitors have rapid activity.
- **Recombinant activated factor VII 7 (rFVIIa)** has been successfully used in patients with acquired haemophilia. It binds to the surface of activated platelets, where it supports thrombin generation and bypass the need for FVIII.
- **Factor Eight Inhibitor Bypassing Agent (FEIBA):** It is a pooled donor product has a mix of several other activated clotting factors

which bypass the factor VIII requiring step in the coagulation pathway, and is prothrombotic, causing MI and DIC in a subset of patients.

- Definitive removal of the auto-antibody by immunosuppression is successful in at least 50% of patients, but carries significant morbidity and mortality in elderly.

**EX**: Old male 70 years with severe epistaxis from both nostrils, Hb 7, ESR 75, normal PT, prolonged PTT, low factor VIII 8 level >>>> Acquired Factor VIII (8) Deficiency >>> Treatment: Recombinant activated factor VII 7 (rFVIIa).

## Hereditary hemorrhagic telangiectasia (HHT)

Also known as **Osler-Weber-Rendu syndrome**.

It is a multisystem vascular dysplasia characterized by the presence of multiple arteriovenous malformations **(AVMs)** that lack intervening capillaries and result in direct connections between arteries and veins.

It is an **autosomal dominant** condition characterized by (as the name suggests) multiple telangiectasia (Small AVMs) over the skin and mucous membranes often rupture and bleed.

About 20% of cases occur spontaneously without prior family history.

May present as iron deficiency anemia secondary to GIT bleeding.

### There are 4 main diagnostic criteria (The Curacao criteria):

- **Epistaxis:** spontaneous, recurrent nose bleeds.
- **Telangiectasis:** multiple at characteristic sites (lips, oral cavity, fingers, nose).
- **Visceral lesions**: for example, gastrointestinal telangiectasia (with or without bleeding which most commonly begins after age 50 years), pulmonary arteriovenous malformations AVM in 30%, hepatic AVM in 30%, cerebral AVM in 20%, spinal AVM.
- **Family history:** a first-degree relative with HHT.

If the patient has **2** >> so they are said to have a **possible** diagnosis of HHT.

If they meet **≥ 3** >> so they are said to have a **definite** diagnosis of HHT.

**N.B:**

| Condition | Bleeding time | PT | PTT | Notes |
|---|---|---|---|---|
| **Vit K Def.** | Unaffected | **Prolonged** | **Prolonged** | 1 normal |
| **Hemophilia** | Unaffected | Unaffected | **Prolonged** | 1 affected |
| **DIC** | **Prolonged** | **Prolonged** | **Prolonged** | All affected |

| Factors | PT | PTT |
|---|---|---|
| 7 (Extrinsic pathway) | **Prolonged** | Unaffected |
| 2 – 5 – 10 | **Prolonged** | **Prolonged** |
| 8 – 9 – 11 – 12 (Intrinsic pathway) | Unaffected | **Prolonged** |

**NB: Prolonged APTT** may be caused by (4): **heparin therapy, haemophilia A or B or acquired factor 8 deficiency, von Willebrand's disease,** or **Antiphospholipid syndrome.**

## Antithrombin III (AT 3) deficiency

Antithrombin III deficiency is an inherited cause of thrombophilia occurring in approximately 1:2,000 of the population. Inheritance is **autosomal dominant.**

Antithrombin III (AT3) is a plasma inhibitor protein that blocks the enzymatic activity of some serine proteases coagulation factors. The activity of this inhibitor is increased by heparin.

Antithrombin III inhibits several clotting factors, primarily thrombin, **factor X and factor IX. It mediates the effects of heparin.**

Heparin works by binding to antithrombin III, enhancing its anticoagulant effect by inhibiting the formation of thrombin and other clotting factors. **Patients with antithrombin III deficiency** may therefore by **resistant to heparin treatment.**

AT3 is synthesised by the **liver**, is **not** vitamin K dependent, and can be **consumed** during **DIC**.

Normal newborns have a reduced activity.

Antithrombin III deficiency comprises a heterogeneous group of disorders, with some patients having a deficiency of normal antithrombin III whilst others produce abnormal antithrombin III.

Patients with **nephrotic** syndrome >>> **loss of AT 3 in urine** >>> ↑ risk of thrombosis (DVT/PE).

### Features:

- **Recurrent venous thrombosis**
- Arterial thrombosis do occur but is uncommon

### Management:

- Thromboembolic events are treated with **lifelong warfarinisation.**
- Heparinisation during pregnancy.
- Antithrombin III concentrates (often using during surgery or childbirth).

**NB**: As patients with antithrombin III deficiency have a **degree of resistance to heparin, so anti-Xa levels should be monitored carefully** to ensure adequate anticoagulation by the LMWH.

## Disseminated Intravascular Coagulation (DIC)

DIC is a complex systemic thrombo-hemorrhagic disorder involving the generation of intravascular fibrin and the consumption of procoagulants and platelets duo to local and systemic activation of coagulation

DIC is caused by the enhanced and abnormally **sustained generation of thrombin**, and is associated **with elevated products of fibrin breakdown**, one of these being ↑ **D-dimer** and **↑FDPs.**

In a recent review by Yu and colleagues, the combination of the **D-dimer** and the **FDP** assay provides **the most rapid** and **specific** diagnosis of DIC.

**Organ failure** is a common finding, being as common as **bleeding** in DIC, and is likely to be due to fibrin deposition within the organ.

Secondary bursts of thrombin formation seen in DIC are instigated by the **intrinsic pathway.**

## DIC is associated with the following:

- **Falling platelet count,**
- **Prolonged PT,**
- **Prolonged PTT**
- **Decreased fibrinogen,**
- **↑FDPs**
- **↑ D-Dimer.**
- **↓ Protein C** - reduced
- **↓ Antithrombin** - reduced.
- Associated **MAHA** (Microangiopathic haemolytic anaemia): usually complicate **chronic** rather than acute DIC, it is due to mechanical damage to RBCs from fibrin stands present within the circulation.

But **the clotting factors may be normal**, especially when one considers that the **acute phase response** may shorten the activated partial thromboplastin time (APTT) and increase fibrinogen.

So Normal clotting parameters **don't** effectively **exclude** a diagnosis of DIC.

The presence of DIC significantly increases **mortality** rates in affected patients

Treatment of the underlying cause, for example, sepsis, **does not always lead** to resolution of the condition.

**Where there is no bleeding or thrombosis, blood products are not recommended**, since there is no evidence base for their use, and they expose the patient unnecessarily to the risks of transfusion.

Transfusion of platelets or plasma components in patients with DIC should **not** be primarily based on laboratory results and should in general be reserved for patients who present with **bleeding**. Hence the most useful parameter for deciding whether this patient requires active treatment would be the **presence or absence of bleeding.**

Where there is bleeding, blood products should be used to gain haemostasis.

## Treatment:

**Blood products replacements:**

- **Cryoprecipitate**: (**If** Fibrinogen <100mg/dl) or significant bleeding.
- **PLT TX:** (Only **If** PLT count < 50) the goal is greater than 20000 or greater than 50000 for serious bleeding.
- **FFP:** (**If** PT and PTT > 1.5 upper limit with significant bleeding.
- **PRBCs**

As a general rule, treatment with blood products in DIC is **not indicated unless** life-threatening **bleeding** occurs or if an invasive procedure is planned.

**In some cases of refractory bleeding despite administration of blood products, administration of low dose heparin can be considered (heparin interfere with thrombin thus reduce the clotting process and consequently consumption of coagulation factors and platelets.**

**Do not administer boluses only infusion is allowed(5 mg/kg/hr) and titrate accordingly.**

**Do not administer if platelet count less than 50000 or there is internal bleeding.**

**To correct a coagulopathy you need to aim for:**

- Fibrinogen >1.0 g/L **>>>** by TX of **Cryoprecipitate**.
- Platelets >50 $\times 10^9$/L **>>>** by TX of **PLT**.
- PT and APTT <1.5 upper range of normal **>>>** by TX of **FFP**.

**EX:** pregnant female with **abortion** and severe vaginal bleeding, **Low PLT** 70 ×10 9/L, **prolonged PT** 25 sec, **prolonged PTT** 55 sec, **low fibrinogen** 0.5 g/L (N= 2-4) **>>>>** **DIC** **>>>>** **Cryoprecipitate** (Fibrinogen replacement infusion).

**When bleeding** is the major problem, the aim is to maintain the prothrombin and activated thromboplastin time **at a ratio of 1.5 times of the control** and the **fibrinogen level above 1 g/L.**

**EX:** A 26-year-old woman presented at 35 weeks of pregnancy with profuse vaginal bleeding. She had suffered two previous miscarriages.
She had a pulse of 95 bpm, BP 110/84 mmHg and no fetal heart sounds were audible.
Lab: ↓Hb **9**, ↓PLT **66**, ↑PT **22**, ↑PTT **55**, ↓Fibrinogen **0.5** (N= 2-4 gm/L).
This is **DIC** >>> treatment: **Cryoprecipitate (Fibrinogen replacement infusion).**
When bleeding is the major problem, the aim is to maintain the PT and PTT at a ratio of 1.5 times of the control and the fibrinogen level above 1 g/L.
Platelet transfusion is recommended if the count is less than 50 ×109/L.

Anaemia is not very severe so in this case fibrinogen replacement would be the appropriate first choice with blood transfusion an addition if bleeding continues and patient develops hypovolaemic shock.

The commonest cause of **chronic DIC** in an **elderly** man with **prostatic** symptoms is **prostate cancer**, the presence of immature red (nucleated RBCs) and white (metamyelocytes and myelocytes) cells in the blood is known as **leucoerythroblastic blood film**, and is often seen in cases of bone marrow invasion and is relatively frequently present in **metastatic prostatic cancer**, particularly hormone-resistant case.

**EX:** Old male 80 years has **easy bruising, loss of weight, jaundice, prostatism**, Lab: TLC 11, **Hb 8, PLT 55, prolonged PTT, low fibrinogen, blood film** shows fragmented schistocytes, nucleated **RBCs,** metamyelocytes and myelocytes >>> The most likely diagnosis is **chronic DIC due to prostate cancer.**

## Von Willebrand's disease (vWD)

It is **the most common inherited bleeding disorder.**

Von Willebrand factor binds platelets to subendothelial surfaces, help platelets to aggregate and prolong the half life of factor 8.

That's why deficiency of this factor manifest mostly with platelet type mucosal bleeding rather than deep bleeding like in coagulation factors.

The vWF gene is located near the tip of the short arm of chromosome 12.

The majority of cases are inherited in an **autosomal dominant** fashion and characteristically behaves **like a platelet disorder** i.e., epistaxis and menorrhagia are common whilst hemarthroses and muscle hematomas are rare.

Males and females are equally affected, although the disease manifestations are more obvious in the females due to menstruation and the associated menorrhagia.

### Role of von Willebrand factor (vWF):

- **Large** glycoprotein which forms up to 1,000,000 Da in size
- Promotes **platelet adhesion** to damaged endothelium.
- **Carrier molecule for factor VIII.**

### Types of vWD:

- **Type 1: partial quantitative deficiency** in vWF (**80%** of patients) (**most common**).
- **Type 2: qualitative deficiency** (abnormal form) of vWF.

- **Type 3:** total deficiency (lack) of vWF (autosomal recessive) (**most severe**).

## Investigation:

- Prolonged bleeding time.
- **APTT** may be prolonged/slightly prolonged (in **50%** of patients).
- **Factor VIII levels may be mild/moderately reduced** (much ↓in haemophilia A)
- vWF levels: are variable and can be influenced by a number of factors, therefore a single level of vWF within the normal reference range does not exclude the diagnosis of vWD.
- **vWF antigen level** concentration in plasma: detected by quantitative immunoassay or ELISA, it is variably reduced, and also can be normal.
- **vWF activity assay**: the degree of platelet agglutination is proportional to the concentration of vWF in the plasma, it is reduced in vWD.
- Defective platelet aggregation with ristocetin: Ristocetin is an antibiotic that causes vWF to bind to and activate platelets, platelets rapidly agglutinate in response to ristocetin but the presence of vWF is necessary for this reaction to occur.
- New test: **PFA-100**: it has 95% sensitivity to diagnose VWD.

To assess the **bleeding tendency** pre procedure for patient with von Willebrand's disease (vWBD), the most useful test in practice is to do the **vWF antigen and activity**; but you would also do **plasma F VIII c activity**.

## Management:

1) **Tranexamic acid (Cyclokapron ®):** It is anti-fibrinolytic drugs for mild bleeding.
   **Tranexamic acid** is a synthetic derivative of lysine. Its primary mode of action is as an antifibrinolytic that reversibly binds to lysine receptor sites on plasminogen or plasmin. This prevents plasmin from binding to and degrading fibrin.

   Tranexamic acid is most commonly prescribed to help treat menorrhagia.

   The role of tranexamic acid in trauma was investigated in the CRASH 2 trial and has been shown to be of benefit in bleeding trauma when administered in the first 3 hours. Tranexamic acid is given as an IV bolus followed by an infusion in cases of major haemorrhage.

   There is also ongoing research looking at the role of tranexamic acid in traumatic brain injury.

2) **Desmopressin (DDAVP) (Vasopressin):**
   - It may be given to increase the amount of the vWF long enough for surgery or dental procedures to be performed.
   - It can provide a **2 fold to 5 fold** increase in plasma **vWF** and **factor VIII** concentrations.
   - It induces cAMP-mediated **vWF secretion** by a direct effect on **endothelial cells** (from Weibel-Palade bodies in endothelial cells).
   - It is similar to ADH, so SE is hyponatraemia.
   - Vwf product in sever bleeding.
3) For severe disease or prior to major surgery (like appendectomy): you would use a **von Willebrand factor concentrate (Humate-P®)**, i.e. **intermediate purity (vWF rich) factor VIII**, which contains the highest concentration of vWF. (**NOT** factor VIII concentrate).

**NB**: **Intermediate** purity factor VIII (containing **high** amount of vWF)
High purity factor VIII (containing lower amount of vWF)
So Purified or recombinant preparations are avoided since they contain only small concentrations of vWF.

**NB**: Factor VIII concentrate, cryoprecipitate, FFP (should be avoided when possible to minimise the risk of transfusion acquired viral illnesses).

**EX**: A 14-year-old boy presents with excessive bleeding from a tooth cavity following an extraction at the dentist.

His investigations show: CBC: normal, PT: normal, slightly elevated PTT 45 sec (N= 30-40), slightly low Factor VIII 45 U/dL (N= 50-150).

The most likely diagnosis is >>> **vWD**

Factor VIII is only slightly reduced in vWD as von Willebrand factor is a protective carrier for factor VIII.

**NB: In haemophilia A >> there is much less factor VIII and much more prolonged PTT than described in VWD.**

**EX**: Pt known to have type 1 von Willebrand's disease will have a tooth extraction >> the most appropriate management to reduce the risk of bleeding is >> **Desmopressin (DDAVP) and tranexamic acid.**

**EX**: A 21-year-old lady diagnosed with severe type 1 von Willebrand disease is planned to undergo emergency appendectomy >>> **Intermediate purity factor VIII.**

## Haematological malignancies: genetics

The common **translocations** associated with hematological malignancies:

### t (9;22) - Philadelphia chromosome:

- Present in **> 95%** of patients with **CML**
- This results in part of the Abelson proto-oncogene being moved to the BCR gene on chromosome 22.
- The resulting BCR-ABL gene codes for a fusion protein which has tyrosine kinase activity in excess of normal.
- Also present in around **25%** of **adult ALL** cases also have this translocation.
- Poor prognostic indicator in ALL and AML.

### t (15;17):

- Seen in **acute promyelocytic leukaemia (M3) of AML.**
- Fusion of PML and RAR-alpha genes

### t (8;14):

- Seen in **Burkitt's lymphoma**
- **MYC** oncogene is translocated to an immunoglobulin gene

### t (11;14):

- **Mantle cell lymphoma**
- Deregulation of the cyclin D1 (BCL-1) gene.

### t (14;18)

- follicular lymphoma
- increased BCL-2 transcription

## Hematological malignancies: infections

### Viruses

- EBV: Hodgkin's and Burkitt's lymphoma, nasopharyngeal carcinoma
- **HTLV-1: Adult T-cell leukaemia/lymphoma**
- HIV-1: High-grade B-cell lymphoma

### Bacteria

- Helicobacter pylori: gastric lymphoma (MALT)

### Protozoa

- malaria: Burkitt's lymphoma

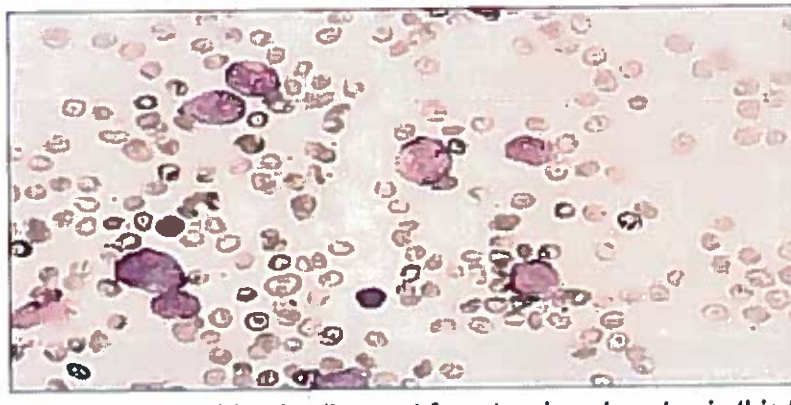
# Acute myeloid leukemia (AML)

Acute myeloid leukemia is **the more common form of acute leukemia in adults.**

It may occur as a **primary** disease or **following a secondary transformation** of a myeloproliferative disorder e.g., CML, myelofibrosis.

## Presentation:

- Vague and non-specific (flu-like symptoms)
- Due to **pancytopenia** (Infection, anaemia, bleeding)
- Splenomegaly may occur but typically mild and asymptomatic.
- LN swelling is rare.
- High TLC leads to leucostasis and hyperviscosity >> drowsiness and retinal vein dilatation.
- Blood film reveals white cells predominantly **myeloblasts** and **promyelocytes.**



AML: Note that all the blood cells apart from two lymphocytes in this film are abnormal and are myeloblasts. One of them contains an Auer rod.

## Poor prognostic features:

- **> 60 years**
- **> 20% blasts** after first course of chemo
- **Cytogenetic: deletions of chromosome 5 (5q-) or 7 (7q-)**

**AML >>> Cytogenetics Karyotype of BM it is of most prognostic value.**

## Good prognostic features

- Karyotype of bone marrow
  - patients with t(8:21) or chromosomes 16 inversion have a low risk of relapse

## Classification - French-American-British (FAB):

- MO - undifferentiated
- M1 - without maturation
- M2 - with granulocytic maturation
- **M3 - acute promyelocytic (APML)**
- M4 - granulocytic and monocytic maturation
- **M5 - monocytic**
- M6 - erythroleukaemia
- M7 - megakaryoblastic

**ALL** cells characteristically stain positive for **PAS** (Periodic acid-Schiff) and **NSE** (Non-specific Esterase).
**AML** cells characteristically stain positive for **Sudan Black** and **myeloperoxidase**, but **M4** and **M5** cells stain positive for **NSE**, while M6 cells stain positive for PAS.

### Differentiating between ALL and AML

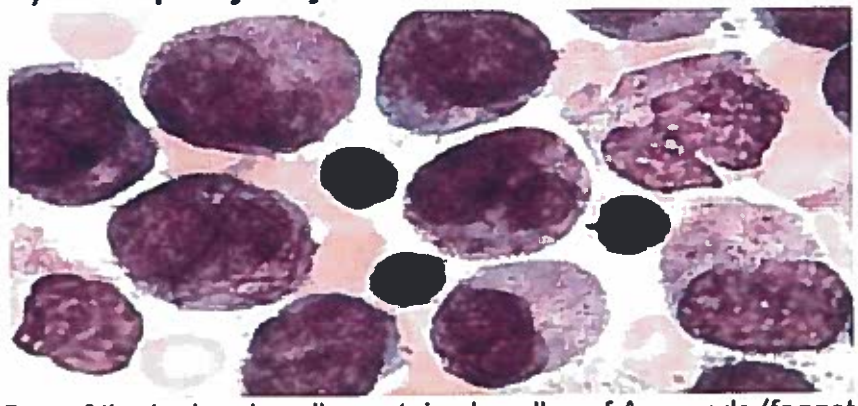
| | ALL | AML |
|---|---|---|
| Presence of auer rods in blood | None | Always present |
| Presence of lymphoblasts in blood | Always present | May or may not be present |
| Bone and joint pain | More commo | Less common |
| Hepatosplenomegaly | More commo | Less common |
| Organ infiltration | More commo | Quite unusual |

## Acute promyelocytic leukaemia (APML) M3:

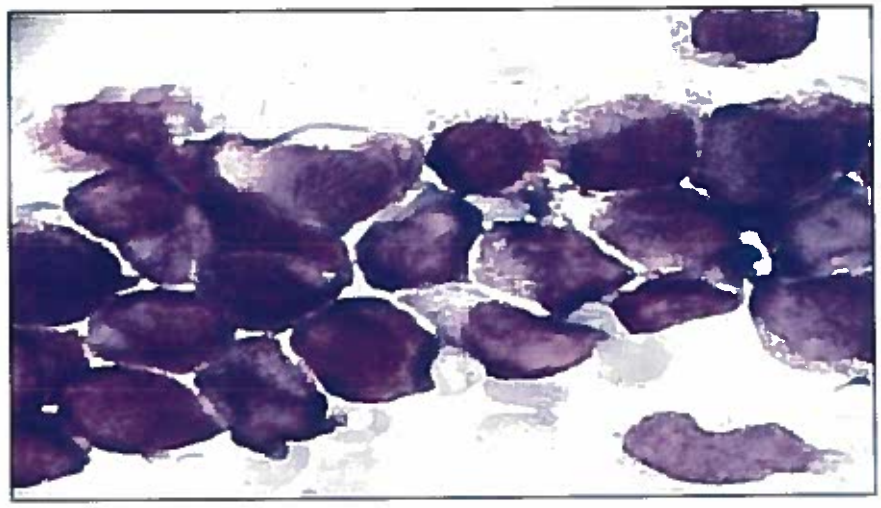
**The importance of identifying APML lies in both the presentation (classically disseminated intravascular coagulation) and management.**
APML is associated with the t(15;17) translocation which causes fusion of the PML and RAR-alpha genes.

- **Good prognosis.**
- It is characterized by a chromosomal translocation involving the **retinoic acid** receptor-alpha gene on chromosome 17 (RARA).
- In 95% of cases, retinoic acid receptor-alpha (**RARA**) gene on chromosome **17** is involved in a reciprocal translocation with the promyelocytic leukemia gene (**PML**) on chromosome **15**.
- Associated **with t (15; 17).**
- The mechanism underlying leukemogenesis is **aberrant fusion of 2 genes** PML and RARA.
- Presents **younger** than other types of AML (average = **25** years old).
- **Auer rods** (seen with myeloperoxidase stain).
- **DIC** (FDPs & D-Dimer) or **thrombocytopenia often at presentation.**

## AML (M3): Acute promyelocytic leukemia



- One of the leukemic cells contains bundles of Auer rods (faggot cell) (arrow).
- Leukemic cells may contain one or multiple Auer rods in their cytoplasm. (Romanowsky stain, XI000)



- It is usually associated with a t (15;17) translocation.
- The slide in this question shows promyelocytes: the cells have large, dark-staining nuclei and granular cytoplasm; the rod-shaped projections in the cells are Auer rods.
- Promyelocytes cytoplasm is heavily granulated. These granules contain pro-coagulant factors that render patients with APL susceptible to the development of DIC.
- Despite this, APL has the best prognosis of all the subtypes of AML.
- Unlike the other AML subtypes, APL is treated with all-trans retinoic acid (ATRA).

**Treatment of AML:** Combination chemotherapy including arabinosylcytosine after apheresis.

**Treatment of APML:** (differs from that of all other AML forms): **All-trans-retinoic acid (ATRA)**; a derivative of **vitamin A**.

**AML** is differentiated from ALL by the presence of **Auer rods** which are **eosinophilic needle-like cytoplasmic inclusions found in blast cells** and which are **pathognomonic of AML**.

**NB**: In AML >> **chromosomal abnormalities** detected by **cytogenetics** are the single most important **prognostic** factor.

**EX:** Male 55 yrs. Hb=8.6 g/dl, PLT= 42 * $10^9$/l, TLC= 36.4 * $10^9$/l, Blood film shows 30% myeloid blasts with Auer rods >>> so AML, good prognosis: t(15;17) i.e M3.
**EX:** A patient with AML develops **jaundice** and **spiking pyrexia** 3 weeks into induction chemotherapy. The patient **remained pyrexial after 7 days of IV antibiotics.**
What is the likely diagnosis >>> **CMV (Cytomegalovirus)**
The most likely cause for the **persisting pyrexia** plus **hepatitis** in this **immunocompromised** patient treated with **appropriate antibiotics** would be a **CMV** infection.

AML (**monocytic**) **M5**: **high count of circulating blasts** >>> may lead to symptoms of cellular hyperviscosity (headache, confusion, **fits**, coma) and tissue deposits of leukaemia cells **(gums hypertrophy)** with cells stain positive with **Sudan Black** and **myeloperoxidase** plus **NES.**

## Acute lymphoblastic leukemia (ALL)

It causes damage and death by crowding out normal cells in the bone marrow and by metastasizing.

ALL is most common in childhood with a peak incidence at 2-5 years of age, and another peak in old age.

The overall cure rate in children is about 80% and about 45-60% of adults have long term disease-free interval.

Acute → relatively short course of the disease, being fatal in as little as a few weeks if untreated.

Terminal Deoxynucleotide Transferase (**TDT**) is present in 95% of ALL.

## Classification (The WHO classification)

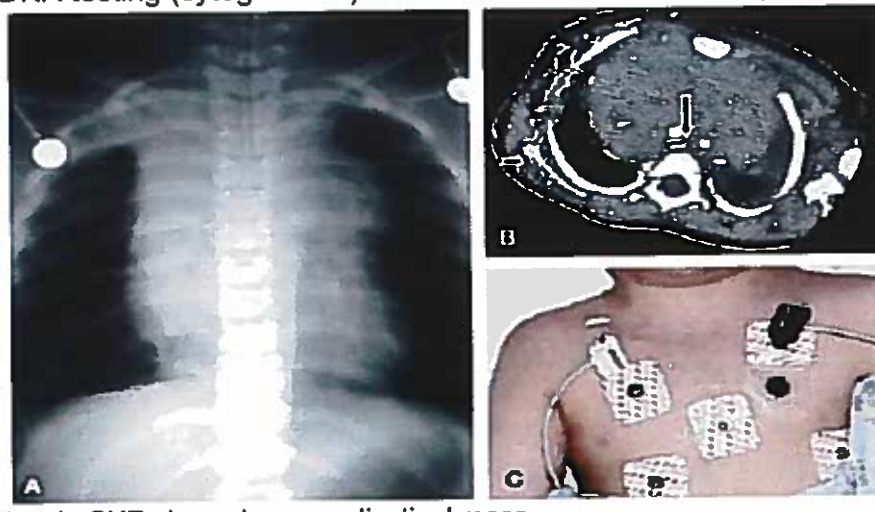
- B-cell ALL (around 80–85% of cases)
- T-cell ALL (around 15–20% of cases)

## Presentation:

- Not specific
- Variable symptoms and signs
- Related to Bone marrow infiltration and/or organ infiltration
- The most common translocation is t(12:21) → good prognosis
- Others like Philadelphia chromosome t(9:22) & t(4:11) → bad prognosis.
- Dyspnoea due to lung infiltration
- Hepatosplenomegaly and lymphadenopathy

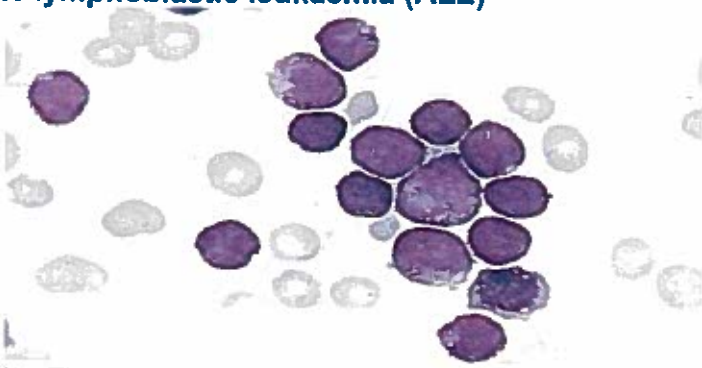
## Investigations:

- Leukocytosis.
- Blast cells are seen on blood smear in 90% of cases
- Bone marrow biopsy is conclusive proof of ALL
- LP to detect CNS involvement
- CXR to look for mediastinal mass
- U&E to look for tumour lysis syndrome
- Immunophenotyping to establish the blast cells origin is B or T lymphocytes.
- DNA testing (cytogenetics) as different mutations reflect prognosis




- A, CXR shows large mediastinal mass.
- 8, CT scan shows narrowing of the trachea caused by mechanical compression of the mediastinal mass (long arrow).
- C, Signs of superior vena cava syndrome include edema of the neck and increased collateral circulation in the chest

## Acute lymphoblastic leukaemia (ALL)



- The lymphoblasts are large with nucleoli.
- There Is very little cytoplasm and no granularity.

### Good prognostic factors:

- Common ALL
- **Pre-B phenotype**
- Low initial WBC
- (FAB) L1 type
- del(9p)

### Poor prognostic factors:

- **FAB L3 type**
- T or B cell surface markers
- **Philadelphia translocation, t(9;22)**
- **Age** < 2 years or > 10 years
- **Male** sex
- **CNS** involvement
- **High** initial WBC (e.g. **> 100 * 109/l)**
- Non-Caucasian

### Treatment

- Before ALL treatment with chemotherapy, if blast cells count is very high (> 100 * 109/l) >> the patient needs **Leukapheresis** to prevent sludge in of capillary beds, this can be life-saving.
- **Philadelphia positive ALL:**
  - **Chemotherapy + rituximab + Tyrosine Kinase Inhibitor**
    - **high dose chemotherapy** (usually UKALL 14 or hyper-CVAD), **together with** the anti-CD20 monoclonal antibody **rituximab and** a **tyrosine kinase inhibitor** in view of the BCR-ABL positivity.
- Central nervous system (CNS) therapy (intrathecal) is indicated in all patients with ALL

- **Lumber puncture (LP) should be delayed until chemotherapy has begun**
- Allogeneic stem cell transplantation

**N.B**: Before ALL treatment with chemotherapy, if blast cells count is very high (**> 100** * $10^9$/l) >> the patient needs **Leukapheresis** to prevent sludge in of capillary beds, this can be life-saving.

## Chronic lymphocytic leukaemia (CLL)

CLL is caused by a **monoclonal proliferation** of well-differentiated **lymphocytes** which are almost always **B-cells** (99%).

**CLL** is the **most common adult leukemia** in western world.

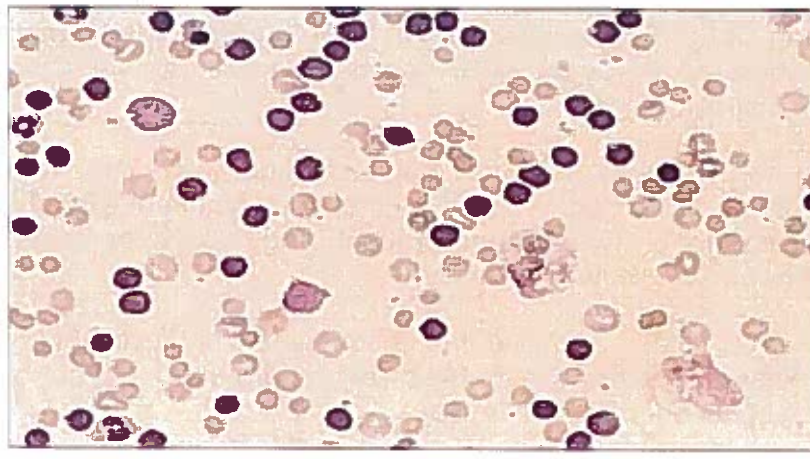
**CLL + anaemia with positive Coombs test >> autoimmune haemolytic anaemia (AHA) >> Prednisolone is the initial intervention of choice. rituximab is the second-line step.**

### Features:

- **Often none**
- It can be discovered incidentally.
- Constitutional: anorexia, weight loss, fever, chest infection
- Bleeding, infections
- Lymphadenopathy more marked than CML
- Hepatosplenomegaly

**Chronic lymphocytic leukaemia (CLL)**

- There is intense facial erythema of CLL.
- Disseminated cutaneous lesions in a patient with CLL who developed fatal varicella despite rapid initiation of IV acyclovir therapy, Varicella lesions are numerous and haemorrhagic.



- There is a predominance: of mature lymmphocytles. These have very little cytoplasm and no nucleoli.
- There are a few smear cells, a degree of polychromasia due to a rieticulocytosis In the presence of autoimmune haemolysis.

## Complications:

- **Pan-Hypogammaglobulinemia** leading to **recurrent infections** >> most common cause of death.
- **Warm AIHA autoimmune hemolytic anemia** in **10-15%** of patients.
- Transformation to high-grade lymphoma (Richter's transformation).

### Richter's transformation

Ritcher's transformation occurs when leukaemia cells enter the lymph node and change into a high-grade, fast-growing non-Hodgkin's lymphoma. Patients often become unwell very suddenly.

**Ritcher's transformation is indicated by one of the following symptoms:**

- lymph node swelling
- fever without infection
- weight loss
- night sweats
- nausea
- abdominal pain

## Investigations

- **CBC: High TLC with lymphocytosis** and **anemia.**
- **Blood film**: **smudge cells**; which are artefacts due to damaged lymphocytes during the slide preparation.
- **Immunophenotyping (flow cytometry):** It is investigation of choice. It will demonstrate the cells to be B-cells (**CD 19** positive). **CD 5** and **CD23** are also characteristically positive.

**Anaemia in CLL:** may be secondary to **bone marrow involvement**, **splenic sequestration of RBCs** or **AIHA** associated with a +ve Coomb's test, spherocytosis, ↑MCV, ↑ RTX.

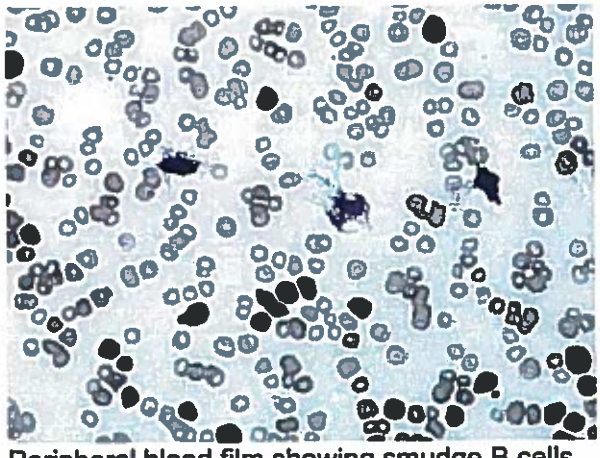
According to Guidelines on the diagnosis and management of CLL, a definitive diagnosis of CLL is based on the combination of a **lymphocytosis** and **characteristic lymphocyte morphology** and **peripheral blood immunophenotype (flow cytometry).**

A bone marrow (BM) is invasive and is sometimes not involved in low grade lymphoproliferative disorders and similarly there may be no cytogenetic abnormality. **(NO need for BM in CLL)**

**CLL >>> Immunophenotyping (flow cytometry):** is investigation of choice.

EX: Old pt. with Hb 8, NN anemia, **TLC 25,000**, ↑ **lymphocytes**, PLt 100 **>>>? CLL**

He is never going to be cured from this condition, and therefore **it would not be necessary to delay/cancel elective surgery for him**. He may be slightly more at risk of infection, due to immune dysfunction that accompanies these conditions, and the surgeons should be aware of this.



Peripheral blood film showing smudge B cells

## Management:

It is a low-grade condition, and does not require immediate treatment; patients undergo a period of **long observation** before any treatment is indicated.

There is no cure in this age group for CLL, therefore no benefit to early treatment.

### Indications for treatment:

- **Progressive marrow failure compromise**: the development or worsening of **anaemia, neutropenia** and/or **thrombocytopenia.**
- **Progressive lymphocytosis: > 50% rate of increase over 2 months or lymphocyte doubling time < 6 months.**
- Massive (>10 cm) or progressive **lymphadenopathy**.
- Massive (>6 cm) or progressive **splenomegaly**.
- **Systemic B symptoms**: weight loss > 10% in previous 6 months, fever >38°C for > 2 weeks, **extreme fatigue, night sweats.**
- **Autoimmune** complications e.g. **autoimmune haemolysis** (spherocytosis, ↑bilirubin, ↑LDH and positive direct Coombs' test) or **ITP.**

## Management:

- Patients who have no indications for treatment are **monitored** with regular CBC.
- **(FCR)** Fludarabine, Cyclophosphamide and Rituximab has now emerged as the initial treatment of choice for the majority of patients.
- **IVIG** to produce a rapid rise in the platelet, it usually has effect in about 48 hours.

**NB:** Patients on **Fludarabine (CLL)** are at increased risk of infection with **pneumocystis carinii pneumonia (PCP)**; for this reason they are recommended to take prior to ttt a **prophylaxis** with either **Co-trimoxazole** or **monthly nebulised pentamidine**.

## Prognostic factors:

### Poor prognostic factors (median survival 3-5 years):

- **Male sex**
- **Age > 70 years**
- **Lymphocyte count > 50**
- **Lymphocyte doubling time < 12 months**
- Prolymphocytes comprising more than 10% of blood lymphocytes
- **Raised LDH**
- **CD38 expression positive**

## Chromosomal changes:

- Deletion of the long arm of chromosome 13 (**del 13q**) is the most common abnormality, being seen in around **50%** of patients. It is associated with a **good** prognosis.
- Deletions of part of the short arm of chromosome 17 (del 17p) are seen in around 5-10% of patients and are associated with a poor prognosis.

**NB:** An **observation policy** is usual during the **early** stages of the disease. **Recurrent infections** are recognized in CLL due to **hypogammaglobulinaemia** and immune paresis; but are not an indication for disease control.
Pt with CLL is likely to benefit from regular infusions of **IVIG** to prevent infections.

# Chronic myeloid leukemia (CML)

## Pathophysiology

The **Philadelphia chromosome** is present in more than **95%** of patients with chronic myeloid leukemia (CML).

It is due to a translocation between the long arm of chromosome 9 and 22 - **t(9:22)**(q34; q11).

This results in part of the ABL proto-oncogene from chromosome 9 being fused with the BCR gene from chromosome 22.

The resulting **BCR-ABL gene codes** for **a fusion protein** which has **tyrosine kinase activity in excess of normal**.

## Etiology

- Idiopathic (in most cases)
- Ionizing radiation (e.g., secondary to therapeutic radiation)
- Aromatic hydrocarbons (especially benzene)

## Presentation:

- **Middle-age (40-50 years).**
- **Anemia, weight loss, abdomen discomfort.**
- **Marked splenomegaly.**
- **Myeloid cells** spectrum is seen in **peripheral** blood.
- **Decreased** leukocyte alkaline phosphatase.
- May undergo blast transformation (AML in 80%, ALL in 20%).

## Investigations

### Peripheral blood

- **spectrum of myeloid cells seen**
  - The blood film shows both mature (neutrophils) and immature forms in various stages of differentiation (myelocytes and metamyelocytes)
    - In acute myelogenous leukemia (AML) one would expect only immature blasts.

- CML causes the most severe leukocytosis (> 500,000/µl) of all forms of leukemia
- Increasing basophilia is a sign of acceleration!

**Cytogenetic analysis of the patient's bone marrow**

- the most useful test
- most cases of CML are usually associated with **BCR-ABL translocation**, (Philadelphia chromosome)
- Better than molecular analysis of peripheral blood

**Molecular analysis of peripheral blood**

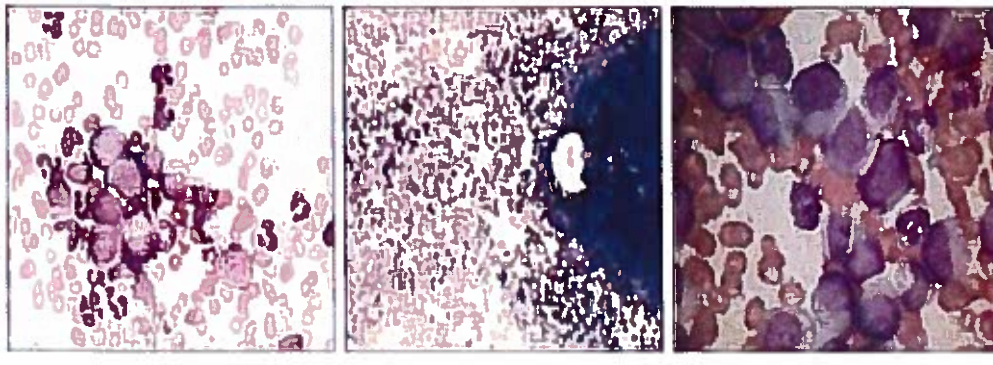
- useful and least invasive for the patient
- BCR-ABL translocation (t[9:22]) can be detected by **PCR**
- **however, in practice one would still eventually proceed to a bone marrow (BM) examination to assess morphology** and you would still also perform conventional cytogenetics on the bone marrow (this is done on a bone marrow sample rather than peripheral blood because the cellularity tends to be greater in the BM, giving lower failure rates of the test).

**Leukocyte alkaline phosphatase (LAP) >> decreased**

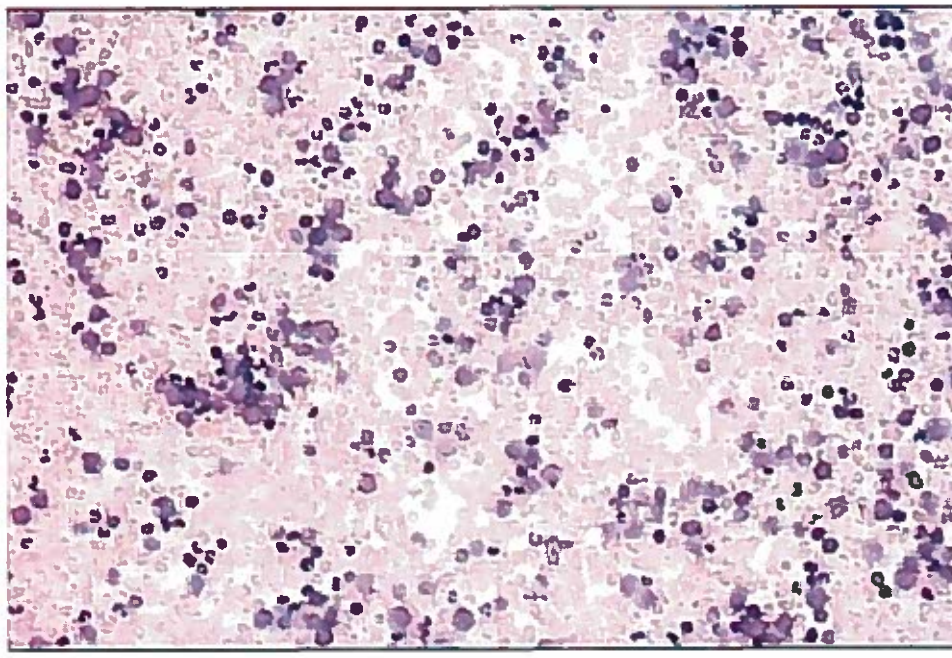
- Low LAP is a distinct feature of CML that distinguishes it from all other forms of leukemia

**WHO classification of the CML phases**

| CML Phase | Blast count in peripheral blood and bone marrow |
|---|---|
| Chronic | < 10% |
| Accelerated | 10–19% |
| Blast | ≥ 20% |



**Hematologic morphology in chronic myelogenous leukaemia (CML):**
A, Peripheral blood in chronic phase disease.
B, Bone marrow in chronic phase disease.
C, Peripheral blood in blastic phase disease.



- The blood film shows both mature (neutrophils) and immature forms in various stages of differentiation (myelocytes and metamyelocytes).
- In acute myelogenous leukemia (AML) one would expect only immature blasts.
- **Treatment**: Glivec (Imatinib).

## Management:

- **Imatinib mesylate (Glivec ®)** 400 mg daily: it is now considered **first-line treatment:** (It is **Tyrosine kinase Inhibitor** associated **with the BCR-ABL fusion defect** and it has very high response rate in chronic phase CML). So it is **Signal transduction inhibitor**. (S.E: **Diarrhea,** oedema, nausea, rash, CHF).
- **Nilotinib** in patients who are Philadelphia chromosome positive and who are intolerant of imatinib.
- Hydroxyurea.
- Interferon-alpha.
- Allogenic bone marrow transplant (the optimum ttt).

**Philadelphia chromosome:**
- Good prognosis in CML,
- Poor prognosis in AML and ALL

# Hairy cell leukaemia

Hairy cell leukemia is a rare malignant proliferation disorder of **B** cells (it is B lymphocytes disorder).

It is usually classified as **a subtype of CML.**

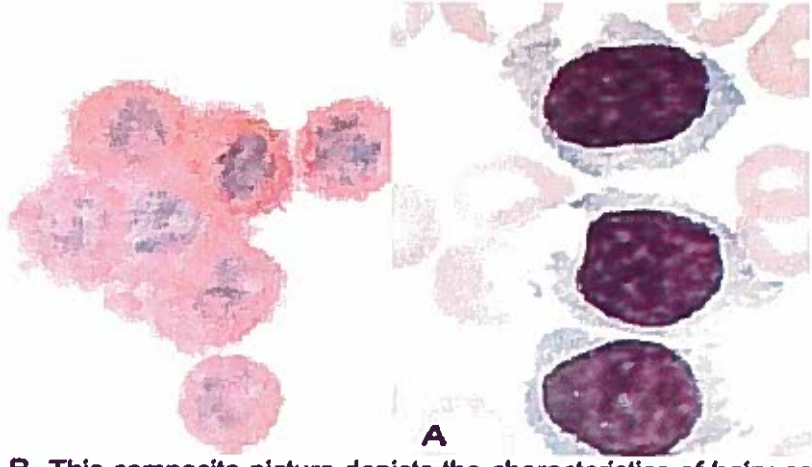
Hairy cells are abnormal WBCs with characteristic hair like projections (microvilli) of cytoplasm when seen by L/M or E/M.

Infiltration of the bone marrow leads to pancytopenia and the patient has hepatosplenomegaly.

It is more common in males (4:1).

## Features:

- **Pancytopenia** (**Monocytopenia** is classical)
- **Large Splenomegaly**
- **Skin vasculitis in 1/3** patients **(cellulitis).**
- **Bone marrow aspirate: 'Dry tap'** despite bone marrow hypercellularity (as in myelofibrosis)
- **Bone marrow biopsy** → shows **"fried egg appearance"**
- The abnormal cells have Tartrate Resistant Acid Phosphatase **(TRAP) stain positive**
- Lymphadenopathy is very uncommon



A

A, B, This composite picture depicts the characteristics of hairy cells, note the typical evenly distributed nuclear chromatin and hairy cytoplasmic projection. Leukemic cells express CD11c (A, Romanowsky stain, 1000; B, immunoalkaline phosphatase stain, 1000)

## Management:

- It **responds dramatically** to the **purine analogue chemotherapy**, is **first-line: cladribine** & **pentostatin**, with resulting survival rates at 5 years of 95-98%.
- Immunotherapy is second-line: rituximab, **interferon-alpha**
- Splenectomy sometimes required.

**Hairy cell leukemia >>> Interferon-alpha:** 2 million U/m2 SC 3 times a week for 12-18 months can be used to salvage relapsed or refractory hairy cell leukemia.

**EX:** Pt with antibiotic resistant **leg cellulitis** and **pancytopenia** >>> Hairy cell leukaemia >>> for bone marrow aspirate (Dry tap) & biopsy (fried egg appearance).

**EX:** Old male 70 years old, **recurrent chest infection**, **large splenomegaly**, **Hb 8**, **TLC 24**, **PLT 25**, **absent monocytes**, blood film shows villous **projections** of atypical monocytes >>> **Hairy cell leukaemia.**

# Leukemoid reaction

The Leukemoid reaction describes **the presence of immature cells such as myeloblasts, promyelocytes and nucleated red cells in the peripheral blood.**

This may be due to infiltration of the bone marrow causing the immature cells to be 'pushed out' or sudden demand for new cells.

## Causes:

- Severe infection
- Severe hemolysis
- Massive hemorrhage
- Metastatic cancer with bone marrow infiltration

A relatively common clinical problem is differentiating chronic myeloid leukemia from a leukemoid reaction. The following differences may help:
Leukemoid reaction:

- ↑ **Leucocyte ALP score(LAP)**
- **'Left shift'** of neutrophils i.e., three or less segments of the nucleus.
- **Toxic granulation (Dohle bodies)** in the white cells.

**Chronic myeloid leukaemia (CML): low** leucocyte alkaline phosphatase score

# Hodgkin's lymphoma

Hodgkin's lymphoma is a malignant proliferation of lymphocytes characterized by the presence of the malignant **Reed-Sternberg cell (RSC)**.
It has a **bimodal age distributions** being most common in the **young adults (15-35 years)** and **elderly** individuals **(> 55 years)**.

| Type | Frequency | Prognosis | Notes |
|---|---|---|---|
| **Lymphocyte depleted** | Rare | **Worst prognosis** | |
| **Lymphocyte predominant** | Around 5% | **Best prognosis** | |
| Mixed cellularity | Around 20% | Good prognosis | Associated with a large number of RSC. |
| **Nodular sclerosing** | **Most common** (around **70%**) | Good prognosis | More common in women. **Associated with lacunar cells.** |

Hodgkin's lymphoma is associated with EBV, 25% of patients have a constitutional upset (night fever, sweats, weight loss, pruritis, lethargy).

## Features

- lymphadenopathy (75%) - painless, non-tender, asymmetrical
- systemic (25%): weight loss, pruritus, night sweats, fever (Pel-Ebstein)
- alcohol pain in HL
- normocytic anaemia, eosinophilia
- LDH raised

## staging

### Ann-Arbor staging of Hodgkin's lymphoma:

- **I:** single lymph node.
- **II:** 2 or more lymph nodes/regions on same side of diaphragm.
- **III:** nodes on **both** sides of diaphragm.
- **IV:** spread beyond lymph nodes extra-nodal organs (liver, BM).

**NB: Spleen** is regarded as a **Lymph Node region,**
**So lymphoma with splenomegaly** >>> Stage **III**

### Each stage may be subdivided into A or B:

- **A** = no systemic symptoms other than **pruritus.**
- **B** = **weight loss** > 10% in last 6 months, **fever** > 38c, **night sweats** (poor prognosis).

### 'B' symptoms also imply a poor prognosis:

- **Weight loss** > 10% in last 6 months
- **Fever** > 38°C
- **Drenching Night sweats**

**NB:** Fatigue and pruritus are not B symptoms, LN mass size and EBV infection although they are common, BUT they have no prognostic significance

## Other factors associated with a poor prognosis:

- Male
- Age > 45 years
- Stage IV disease
- Hb < 10.5 g/dl
- Lymphocyte count < 600/µl or < 8%
- WBCs > 15,000/µl
- Albumin < 40 g/l

## Diagnosis:

- Hodgkin results in **patchy** bone marrow infiltration, an isolated bone marrow biopsy may yield non-specific results.
- Bone marrow biopsy is more useful for **staging** of **advanced** disease.
- **Lymph node biopsy** would be more likely to be positive, **Reed-S Cells** are evident on microscopy.

## Management:

- Early stage (IA or IIA): Radiotherapy and chemotherapy.
- Later stage (III, IVA or IVB): Chemotherapy alone.
- Large mass in chest regardless of stage: Radiotherapy and chemotherapy.
- Chemotherapy includes **ABVD**: **A**driamycin, **B**leomycin, **V**incristine, **D**oxorubicin, cyclophosphamide, prednisolone, Rituximab & others.
- Prognosis is good overall, but it depends on classification and staging.

**Bleomycin related pulmonary fibrosis is a major toxicity of the widely used ABVD regimen.** A **HRCT** scan and **PFTs** are required to diagnose this. Also **Adriamycin** (also known as **Doxorubicin**) can cause **cardiotoxicity**, with evidence of abnormalities on the **ECG** & **Echocardiography**.

**NB: Relapsed Hodgkin lymphoma** in an **early** relapse (less than one year) must be managed aggressively with **salvage chemotherapy** followed by BEAM conditioned **autologous stem cell transplantation** as the established gold standard.

**EX:** A 25-year-old lady with a history of nodular sclerosing Hodgkin lymphoma in remission for 9 months after 6 cycles of ABVD chemotherapy presents again with a one-month history of dry cough.

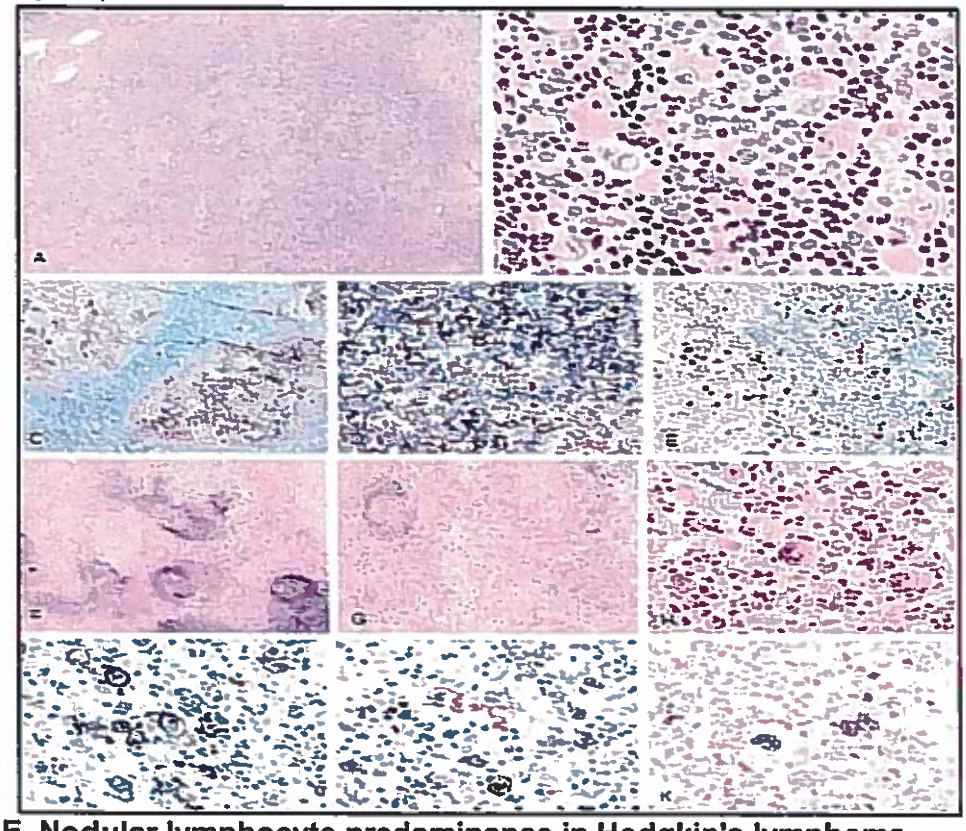
CXR shows mediastinal widening, and PET scanning shows active thoracic disease. Biopsy of the mediastinal mass reveals nodular sclerosing Hodgkin.

What is the most appropriate management option for this lady **>>> Salvage chemotherapy followed by autologous stem cell transplant.**

**Mantle radiotherapy** was introduced during **1960s** for people with **Hodgkin's** disease whose cancer was confined to LNs in the chest, neck or under the arms which aim to give radiotherapy to all **LNs lying above the diaphragm.**
**Women** who were treated with mantle therapy appear to be at a greater risk of developing a **breast cancer** and **hyperthyroidism** (thyroid nodules or malignancy), so they should have **screen** by **breast MRI** and **TFTs.**

## Differential diagnosis:

Reactive lymph nodes seen in IMN, cat scratch fever or drug reaction (phenytoin).



**A-E, Nodular lymphocyte predominance in Hodgkin's lymphoma.**

- A- Large nodules effacing the nodal architecture.
- B- High magnification showing large mononucleated and multilobulated popcorn cells in a background of reactive histiocytes and small lymphocytes.
- C- The nodules are associated with a meshwork of CD21 follicular dendritic cells.
- D-Immunoperoxidase staining for CD20 showing strong positivity of the large neoplastic cells and small B lymphocytes in the background.

- **E-** Immunoperoxidase staining for Bcl-6 showing positivity of the neoplastic cells.
- **F-K**, Classic Hodgkin's lymphoma.
- **F-** Nodular sclerosis type, showing cellular nodules separated by fibrous bands.
- **G-** Mixed cellularity type, showing an interfollicular infiltrate.
- **H-** Classic Reed-Sternberg cells in a mixed reactive background.
- **I-** Immunoperoxidase staining for CD30, showing membrane and focally paranuclear Golgi region staining of Reed-Sternberg cells.
- **J-** Immunoperoxidase staining for CD15, showing membrane and focally paranuclear Golgi region staining of Reed-Sternberg cells.
- **K-** In situ hybridization showing positivity of Reed-Sternberg cells for Epstein-Barr virus RNA (EBER).

| Hodgkin's lymphoma (HL) | Non-Hodgkin's lymphoma (NHL) |
|---|---|
| Younger age | Older age |
| more often restricted to lymph nodes in the neck. | Peripheral lymphadenopathy is common |
| Reed-Sternberg cells are present. | Reed-Sternberg cells are NOT present. |
| Extra-nodal involvement un common | Extra-nodal involvement is common |

## Non-Hodgkin's Lymphomas (NHL)

They are a diverse group of lymphomas that include any kind of lymphoma except Hodgkin's lymphomas.
Types of NHL vary significantly in their severity, from indolent to very aggressive.
**Low**-grade lymphoma is predominantly a disease of **older** people and is more likely to **bone marrow infiltration**.
Most of NHL are of **B cell phenotype**, although T cell tumors are increasingly being recognized.

### Symptoms

- Painless lymphadenopathy (non-tender, rubbery, asymmetrical)
- Constitutional/B symptoms (fever, weight loss, night sweats, lethargy)
- Extranodal Disease - gastric (dyspepsia, dysphagia, weight loss, abdominal pain), bone marrow (pancytopenia, bone pain), lungs, skin, central nervous system (nerve palsies)

While differentiating Hodgkin's lymphoma from non-Hodgkin's lymphoma is done by biopsy certain elements of the clinical presentation can help point towards one rather than the other.

- Lymphadenopathy in Hodgkin's lymphoma can experience alcohol-induced pain in the node

- 'B' symptoms typically occur earlier in Hodgkin's lymphoma and later in non-Hodgkin's lymphoma
- Extra-nodal disease is much more common in non-Hodgkin's lymphoma than in Hodgkin's lymphoma

## Signs

- Signs of weight loss
- Lymphadenopathy (typically in the cervical, axillary or inguinal region)
- Palpable abdominal mass - hepatomegaly, splenomegaly, lymph nodes
- Testicular mass
- Fever

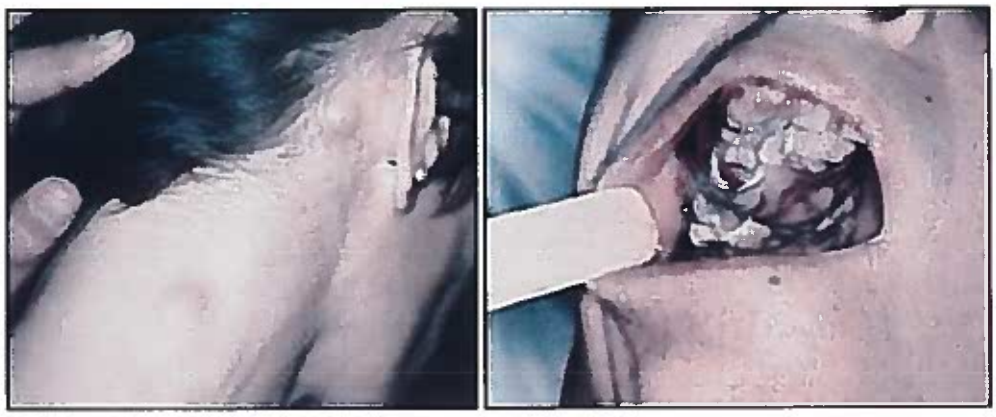
with advanced disease, **bone marrow infiltration** being almost invariable. Anaemia, ↑ TLC and/or ↓ PLT are suggestive of Bone marrow infiltration. **Low grade anaemia** is a more common presenting feature versus pancytopenia.

### Burkitt's lymphoma

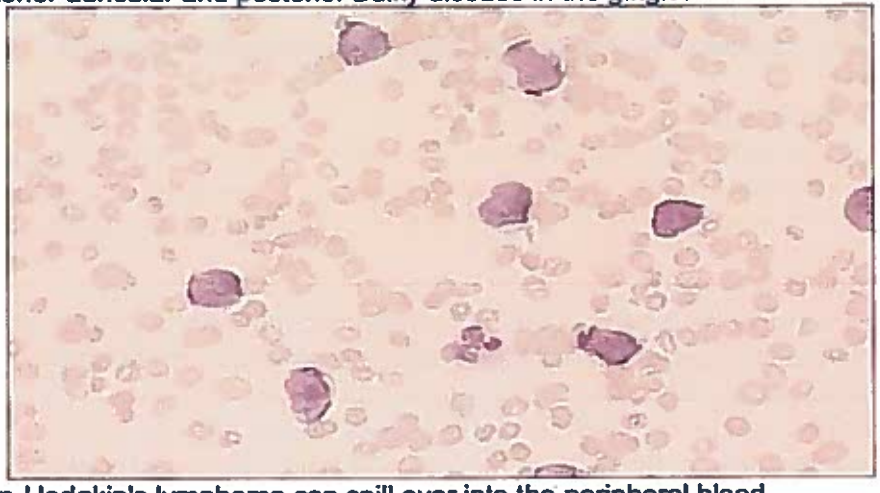
- **Extra-nodal presentation** is more common than Hodgkin's disease.
- **Renal impairment** in NHL usually occurs as a consequence of ureteric obstruction secondary to intra-abdominal or pelvic LN enlargement.

## Investigations

- Excisional node biopsy is the diagnostic investigation of choice (certain subtypes will have a classical appearance on biopsy such as Burkitt's lymphoma having a 'starry sky' appearance)
- CT chest, abdomen and pelvis (to assess staging)
- HIV test (often performed as this is a risk factor for non-Hodgkin's lymphoma)
- FBC and blood film (patient may have a normocytic anaemia and can help rule out other haematological malignancy such as leukaemia)
- ESR (useful as a prognostic indicator)
- LDH (a marker of cell turnover, useful as a prognostic indicator)
- Other investigations can be ordered as the clinical picture indicates (LFT's if liver metastasis suspected, PET CT or bone marrow biopsy to look for bone involvement, LP if neurological symptoms)



Posterior auricular and posterior Bulky disease in the gingiva cervical adenopath



Non-Hodgkin's lymphoma can spill over into the peripheral blood.
These high-grade lymphoma cells can be difficult to distinguish from acute leukaemic cells (note that they are very big and have an irregular nuclear outline)

## Staging

**The most common staging system used for non-Hodgkin's lymphoma is the Ann Arbor system.**

- Stage 1 - One node affected
- Stage 2 - More than one node affected on the same side of the diaphragm
- Stage 3 - Nodes affected on both sides of the diaphragm
- Stage 4 - Extra-nodal involvement e.g. Spleen, bone marrow or CNS

**The stage is combined with the letter A or B** to indicate the presence of 'B' symptoms. With the letter A indicating no B symptoms present and B indicating any of the beta symptoms present. For example, a patient with a single node affected and no 'B' symptoms would be stage 1A.

## Complications

- Bone marrow infiltration causing anaemia, neutropenia or thrombocytopenia
- Superior vena cava obstruction
- Metastasis
- Spinal cord compression
- Complications related to treatment e.g. Side effects of chemotherapy

## Prognosis

- Low-grade non-Hodgkin's lymphoma has a better prognosis
- High-grade non-Hodgkin's lymphoma has a worse prognosis but a higher cure rate

## Management:

- **LN Biopsy** is sufficient for a definitive diagnosis.
- It is essential for modern classification to submit the lymphoid tissue for **immune-phenotyping** and **cytogenetics/molecular analysis**.
- **Chemotherapy** is the main stay of treatment in most cases, but carries associated **risk** of **leukaemia** which peaks around 5 years after original treatment.
- High-grade Lymphoma are responsive to chemotherapy and potentially curable.
- Low-grade Lymphoma are incurable with conventional therapy.

# Burkitt's lymphoma

Burkitt's lymphoma is a **high-grade B-cell neoplasm (NHL)**.
It was first discovered in children in West Africa who presented with a jaw tumor, extra-nodal abdominal involvement and ovarian tumors.

## There are two major forms:

- **Endemic (African) form**: typically involves maxilla or mandible.
- **Sporadic form**: abdominal (e.g. **ileo-caecal**) tumours are **the most common form**. More common in patients with **HIV.**

Burkitt's lymphoma is **associated with the C-MYC gene translocation, usually t (8:14)** which is observed in approximately **80%** of patients with the disease.
The **Epstein-Barr virus (EBV)** is strongly implicated in the development of the African form of Burkitt's lymphoma and to a lesser extent the sporadic form.

**Microscopy findings**: starry sky' appearance: lymphocyte sheets interspersed with macrophages containing dead apoptotic tumour cells

**Management** is with **chemotherapy** (cyclophosphamide, vincristine, methotrexate and prednisolone).
This tends to produce a rapid response which may cause **'tumour lysis**

## MALToma's

MALToma's, also known as marginal zone lymphomas, are low grade lymphomas, most often diagnosed in the stomach.

They are peculiar in that they are often associated with chronic inflammation of some type:

- In the **stomach**, secondary to chronic **H-pylori** gastritis.
- In the **eyes**, secondary to **Sjogren's** syndrome.
- In the **thyroid**, secondary to **Hashimoto's** thyroiditis.
- In the **intestine**, secondary to **Crohn's** or **Coeliac** disease.

- A, Endoscopic US: showing a narrow sheet of low echogenic tissue in the submucosa (arrows).
- B, CT scan in a different patient shows a typical small soft tissue mass in the region of the gastroesophageal junction, the stomach has been fully distended by oral administration of Gastrografin and

**Treatment:** of H-pylori will cause regression of 90% of low-grade gastric MALToma's.

# Multiple Myeloma (plasma cell myloma)

**Multiple myeloma** is a neoplasm of the bone marrow **plasma cells**.

**Myeloma** is a clonal B-cell malignancy characterized by proliferation of plasma cells that accumulate mainly in bone marrow and usually secrete paraprotein.

It accounts for **1%** of all malignancies and **10%** of hematological malignancies.

The peak incidence is patients aged **60-70** years.

Multiple myeloma is a relatively common malignancy that is part of a **spectrum** of disorders ranging from monoclonal gammopathy of unknown significance (MGUS) to plasma cell leukemia.

Gammopathy is a disturbance in the synthesis of immunoglobulins. **Monoclonal gammopathy** suggests there is a single neoplastic clone causing an excess of immunoglobulin.

There is overproduction of immunoglobulin (Ig) usually **IgG** in about **55%**, IgA in about 20%: of these patients, 40% have Bence-John's proteinuria. Light chain is found in 20% of patients, while IgD and IgE myeloma account for about 1% of cases.
**Hyperviscosity syndrome**: the viscosity is directly proportional to the **size** of the molecule causing it; therefore **IgM**, which is pentameric, is most likely to cause hyperviscosity, followed by the dimeric **IgA**, then **IgG**.

An important differential diagnosis is monoclonal gammopathy of unknown significance (MGUS).

**Macroglobulins** are plasma globulins of high molecular weight. They are a central feature of Waldenström macroglobulinaemia, where proliferation of lymphocytes causes an excess of IgM.
This is an important differential diagnosis when multiple myeloma is suspected.
Macroglobulin's are not typically a feature of multiple myeloma.

**Which acid-base disorders may be found in an IgG multiple myeloma?**

**>> Low anion-gap metabolic acidosis**

- **IgG tends to be cationic, whereas IgA tends to be anionic. As a consequence, patients with IgG myeloma will tend to have a lower than normal serum anion gap.**

## Laboratory confirmation of Multiple Myeloma (NICE 2018

**To confirm the presence of a paraprotein Indicating possible myeloma or (MGUS):**

- **Two tests must always be done:** both serum electrophoresis and either serum or urinary free light chains
- **If serum protein electrophoresis is abnormal, use serum immunofixation to** confirm the presence of a paraprotein indicating possible myeloma or MGUS,
- **Do not** use serum protein electrophoresis, serum immunofixation, serum--free light-chain assay or urine electrophoresis (urine Bence-Jones protein assessment) **alone to exclude a diagnosis of myeloma.**
  - **free light chains (20-30% of cases of myeloma)** are found in the absence of a detectable monoclonal protein in the peripheral blood.

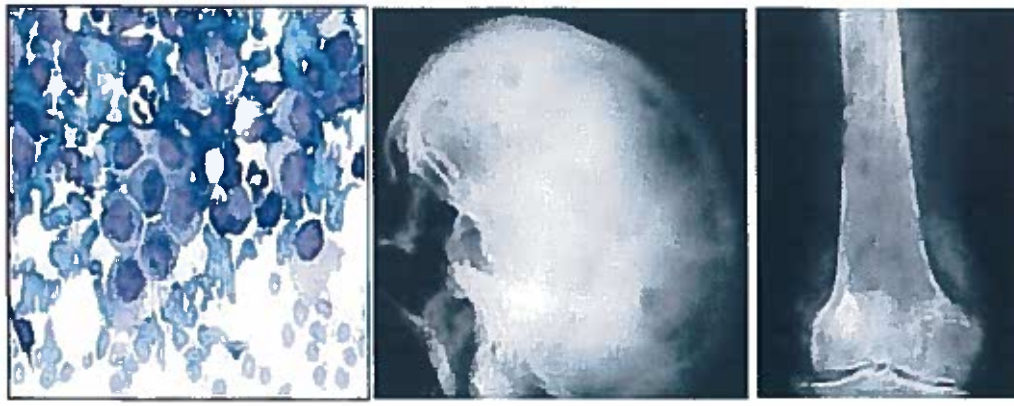
**To. confirm a diagnosis of myeloma;**

- **Bone marrow aspirate** and trephine biopsy
  - Morphology to determine plasma cell percentage (≥10%),
  - Flow cytometry to determine plasma cell phenotype

**Diagnostic Criteria for myeloma** (International Myeloma Working Group 2010): **ALL THREE (3)** are required:

1) **Monoclonal plasma cells in the bone marrow** (involving **>10%** of the bone marrow) and/or presence of biopsy-proven plasmacytoma.
2) **Monoclonal proteins** in the **serum** (Plasma immunoelectrophoretic to look for an M band) and **urine** (Lambda light chains secreted in the urine as Bence Jones protein, this is most accurately detected by urine protein electrophoresis) or light chain immunoglobulins in bone biopsy in any percentage ar as a tumor (plasmacytoma).
3) **Myeloma-related organ dysfunction (≥ 1):**
   A. High serum Calcium (greater than 11.5 mg/dl)
   B. Renal impairment (creatinine more than 2 mg/dl)
   C. Anemia (Hb less than 10 gm/dl)
   D. Bone lesions on the skeletal survey: lytic lesions or osteoporosis (seen in radiographs, PET scan or MRI).
   E. **60% or more colonal plasma cells in bone marrow or a serum free kappa to lambda ratio of greater than 100 or less than 0.01 are also daignostic as they are considered end organ damage.**

**N.B:** Smoldering myeloma is defined as :10-59% clonal plasma cells in the bone marrow, serum paraproteins of 3 grams/dl or higher, without end organ damage.



- A, The cells of myeloma often have a spoked or cartwheel appearance to the chromatin. The nuclei may be centrally located but are more often placed eccentrically within the cytoplasm (Romanowsky stain).
- B, Well-defined punched-out lesions are shown in the skull.
- C, Discrete round or oval lesions in the femur. The whole marrow is probably infiltrated with myeloma. Visible lesions are those which have eroded the cortex. Similar appearances may occur in carcinomatosis.

## Hypercalcemia in myeloma:

- Primary factor: due primarily to **increased osteoclastic bone resorption** caused by local cytokines (e.g., IL-1, TNF) released by the myeloma cells.
- Much less common contributing factors: impaired renal function, increased renal tubular calcium reabsorption and elevated **PTH-rP** levels.

## The hyperphosphatasemia in multiple myeloma:

It is due to reduced renal excretion which may be directly due to renal impairment or interference with excessive protein load.

**Causes** of recurrent infection in myeloma:

- neutropenia.
- underproduction of normal immunoglobulins.
- immunosuppressive treatment.

They are prone to infection with encapsulated organisms (streptococcus and Hemophilus influenza).

## Differential diagnosis:

**This disease must be differentiated from other types of paraproteinemia and benign hypergammaglobulinemia seen in chronic liver diseases and chronic inflammatory status and chronic infections.**

## Treatment:

- **Melphalan** and prednisolone.
- Immunomodulatory drugs such a **thalidomide** and **lenalidomide:** significant improvements in survival may be expected through the addition of it to standard chemotherapeutic regimes. (**Teratogenic**, myelosuppression, somnolence, peripheral neuropathy and constipation)
- **Bortezomib:** inhibits the 26 S proteosome, indirectly inhibiting nuclear factor Kappa and causing apoptosis.
- **Bisphosphonates** reduce bony disease in myeloma, lowering the frequency of pathological fractures. There is also evidence that bisphosphonates modulate the disease and have some anti-tumour activity. **As a result, bisphosphonates should be given routinely to patients with myeloma**, even in the absence of hypercalcaemia.
- **Plasma exchange.**

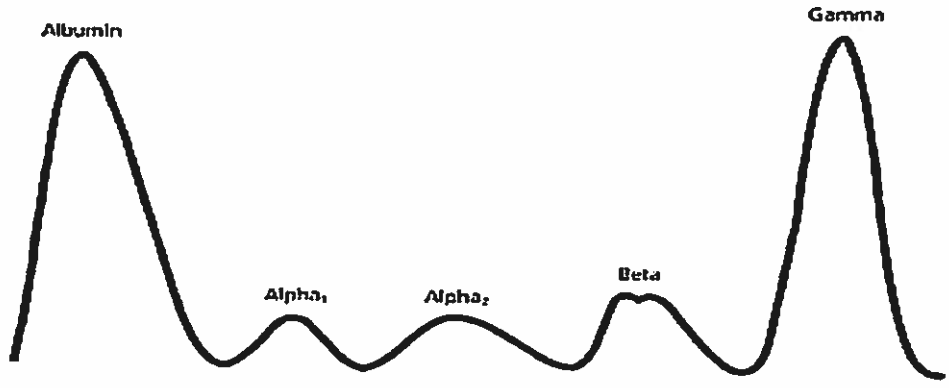
## Myeloma: prognosis:

- **B2-microglobulin** is a useful marker of prognosis - **raised** levels of >3.5 mg/L is strongly implied poor prognosis.
- **Low levels of albumin** are also associated with a poor prognosis.
- Hypercalcaemia
- Severity of anaemia
- Viscosity
- LDH,
- Recurrent bacterial infections.

**International prognostic index:**

| Stage | Criteria | Median survival (months) |
|---|---|---|
| I | B2 microglobulin < 3.5 mg/l<br>Albumin > 35 g/l | 62 |
| II | Not I or III | 45 |
| III | B2 microglobulin > 5.5 mg/l | 29 |

Pt e' **Renal impairment+ Hypercalcemia+ High total protein >> Myeloma.**




**Abnormal serum protein electrophoresis pattern in a patient with multiple myeloma. Note the large spike in the gamma region.**

- In the interpretation of serum protein electrophoresis, most attention focuses on the gamma region(gamma-globulin zone), which is composed predominantly of antibodies of the IgG type.

## Waldenström's macroglobulinaemia (WM)

Waldenström's macroglobulinaemia is an uncommon condition seen in **older** men (70- 80 years). It is a type of **lymphoplasmacytoid lymphoma malignancy**.

It is characterized by the presence of a **high level of a macroglobulin (immunoglobulin M [IgM]),** elevated serum viscosity and the presence of a lymphoplasmacytic infiltrate in the bone marrow, resulting in **pancytopenia**.

Raynaud's phenomenon may herald the onset of this condition and is due to cryoglobulinemia.

The **monoclonal IgM** causes:

- **Hyperviscosity syndrome**
- **Pancytopenia**
- Cryoglobulinemia types 1 and 2
- Coagulation abnormalities >> DVT
- Polyneuropathies
- Cold agglutinin disease
- Primary amyloidosis
- Tissue deposition of amorphous IgM in skin, GIT, kidneys, and other organs.

## Features:

- Systemic upset: weight loss, lethargy **(NO BONY PAINS).**
- **Monoclonal IgM paraproteinaemia**
- **Hyperviscosity syndrome** in around 10-15% of patients e.g., visual disturbance due to **retinal vein thrombosis, DVT.**
- **Hepatosplenomegaly**
- **Lymphadenopathy**
- **Cryoglobulinemia** e.g. **Raynaud's**
- ↑ **ESR**

## Investigations:

- **Bone marrow aspirate** usually shows infiltration with lymph-plasmacytoid cells.
- **Protein electrophoresis** shows an IgM paraprotein (> 20 gm/L).

### Plasma viscosity

- plasma viscosity measurement is essential to diagnose and **initiate treatment.** The initial treatment would be **plasmapheresis** followed by cytoreductive therapy.

### Differential diagnosis

#### multiple myeloma

- usually presents with IgG or IgA secretion and lytic bone lesions.

#### Waldenström's

- **In an elderly patient found to have a large IgM–kappa paraprotein, which feature will help to decide whether it is related to Waldenström's macroglobulinaemia?**
  - **No isotype suppression**
    - Isotype suppression (**normal IgG and IgA levels**) is more a feature of myeloma than Waldenström's macroglobulinaemia and is therefore a good differentiator.

**Death** occurs either:

- due to **cardiovascular** events because of increased viscosity, or
- due to progression of **bone marrow infiltration** leading to suppressed response to **infection**

**Ex:** Old male with a DVT + recently lost weight + Blood tests reveal ↑ IgM : >>> Waldenstrom's macroglobulinaemia.
EX: Old woman has a much raised IgM level, pancytopenia, Raynaud's phenomenon and a foot ulcer >>> Waldenström's macroglobulinaemia.
Waldenstrom's macroglobulinaemia is more likely than MGUS (monoclonal gammopathy of undetermined significance) (given the weight loss and deep vein thrombosis (evidence of hyperviscosity)).
IgM paraproteinaemia >>>? Waldenstrom's macroglobulinaemia.
IgG and IgA are the most common type of immunoglobulins produced in myeloma.

## Management:

- **Alkylating agents:** is the **first** line treatment.
- Young patient may benefit from doxorubicin.
- Monoclonal antibody as rituximab, sometimes in combination with chemotherapeutic drugs: chlorambucil, cyclophosphamide or vincristine.
- Corticosteroids may be used in combination.
- **Plasmapheresis** can be used to treat the **hyperviscosity**, it can rapidly reduce viscosity and risk of thromboembolic events, but it does not address the underlying disease.

**NB**: Causes of hyperviscosity syndrome: Myeloma, Waldenström macroglobulinaemia, (PRV) Polycythemia rubra vera & Leukemia.

# Monoclonal gammopathy of undetermined significance (MGUS)

MGUS is monoclonal paraproteinemia without evidence of end-organ damage.

MGUS, also known as **benign paraproteinemia and monoclonal gammopathy** is a common condition that causes a paraproteinemia and is often mistaken for myeloma.

Differentiating features are listed below.

Patients are at increased risk of developing myeloma.

Around 1% may progress to myeloma annually. Around 10% of patients eventually develop myeloma at 5 years, with 50% at 15 years.

The vast majority of patients can be managed **conservatively**.

Evidence of deteriorating renal function or impaired immunity may indicate that transformation to myeloma has occurred.

## Features:

- Usually **asymptomatic** and picked up **incidentally**.
- **No bone pain** or increased risk of infections.
- **No end organ damage.**
- Around 10-30% of patients have a demyelinating neuropathy.

## Differentiating features from myeloma:

- Normal immune function.

- **Normal beta-2 macroglobulin levels.**
- **Lower level of paraproteinaemia than myeloma** (e.g. **≤ 30g/l IgG**, or < 20g/l IgA). (i.e. there is high IgG but not as high as in myeloma).
- Stable level of paraproteinemia.
- **No** Bence John's protein in urine.
- No clinical features of myeloma (e.g., **NO lytic lesions on x-rays, NO hypercalcemia, NO immune paresis or NO renal disease).**
- **NO evidence of end-organ damage.**
- **Plasma cell involvement of bone marrow is only Less than 10%.**

**Normal levels of: IgG** up to **13** gm/L, **IgA** up to **3** gm/L & **IgM** up to **3** gm/L

### Diagnostic criteria:

1) Serum paraprotein < 30 g/l, AND
2) In bone marrow biopsy the Clonal plasma cells < 10%, AND
3) NO myeloma-related organ impairment.

Regular follow up with blood tests only.

## Important hematological drugs

## Heparin

There are two main types of heparin - unfractionated, 'standard' heparin or low molecular weight heparin (LMWH).

Heparin works by binding to antithrombin III then forms a complex which enhancing the antithrombin III anticoagulant effect by inhibiting the formation of **thrombin (factor 2)** and other clotting **factors IXa, Xa, XIa and XIIa (9,10,11,12).**

**Patients with antithrombin III deficiency may therefore by resistant to heparin treatment.**

LMWH however only increases the action of antithrombin III on factor Xa.

Both UFH and LMWH can cause **hyperkalemia**. This is thought to be caused by inhibition of aldosterone secretion.

Heparin overdose may be reversed by **protamine sulphate**, although this only partially reverses the effect of LMWH.

Heparin resistance may be due to **Antithrombin III deficiency.**

The table below shows the differences between standard heparin and LMWH:

| | Standard heparin (UFH) | Low molecular weight heparin (LMWH) |
|---|---|---|
| **Administration** | Intravenous | Subcutaneous |
| **Duration of action** | Short | Long |
| **Mechanism of action** | Activates antithrombin III. Forms a complex that inhibits thrombin, factors Xa, IXa, XIa and XIIa | Activates antithrombin III. Forms a complex that inhibits factor Xa |
| **Side-effects** | Bleeding.<br>HIT.<br>Osteoporosis. | Bleeding.<br>Lower risk of HIT and osteoporosis. |
| **Monitoring** | Activated partial thromboplastin time (**APTT**) | **Anti-Factor Xa** (although routine monitoring is not required) |
| **Notes** | Useful in situations where there is a high risk of bleeding as anticoagulation can be terminated rapidly. | Now standard in the management of venous thromboembolism treatment and prophylaxis and acute coronary syndromes. |

**Protamine sulphate** is the **antidote** for LMWH.
This reverses most, but not all, of the effects of LMWH.
The dose of protamine sulphate given is dependent upon the dose of LMWH administered and the time of administration.
If protamine is given **within 8 hours** of the LMWH then a maximum neutralizing dose is **1 mg** protamine/**100 units (or 1 mg)** of LMWH given in the last dose.
If **more than 8 hours** have passed since the dose of LMWH was given, administer **0.5 mg** protamine per **100 units (or 1 mg)** of LMWH given.
Protamine is administered by **slow IV infusion** (over **10 minutes**) to avoid a hypotensive reaction. Protamine requires a high level of caution when being prescribed and administered.

**Rivaroxaban (Xarelto ®):** is a highly selective direct factor Xa inhibitor.
**Inhibition of factor Xa** interrupts the intrinsic and extrinsic pathway of the coagulation cascade, inhibiting both thrombin formation and development of thrombi.
Rivaroxaban does not inhibit thrombin and that it has no effect on platelets has been demonstrated.
Indications: chronic non-valvular AF.

## USE HAS-BLED SCORE TO ASSESS THE RISK FOR BLEEDING

## Heparin-induced thrombocytopenia (HIT):

It is a severe **Immune mediated** drug reaction that can occur in any patient exposed to **any form heparin occur in 3% of patients exposed to heparin and 0.6% of patients exposed to LMWH** by therapeutic or prophylactic doses or even the minute amounts in heparin flushes and on heparin-coated catheters.

**Antibodies** usually develop after a patient has been on heparin for 5 or more days, but may develop sooner if there has been previous heparin exposure.

The antibodies-heparin complex activates the platelets independent on the physiologic hemostasis. this causes thrombosis and thrombocytopenia.

Usually does not develop until **after 5 -14 days of exposure to heparin.**

Despite being associated with **low platelets, bleeding is rare.** HIT is strongly associated with **thrombosis.** HIT is actually a **prothrombotic** condition (DVT, PE, MI, CVS, limb artery occlusion) thrombosis can be detected in up to 50% of patients up to 30 days post diagnosis.

Features include a **greater than 50% reduction in platelets** (e.g. from 490 to 200x109/L), **thrombosis** and **skin allergy.**

## Types:

### Type I HIT:

- It is a non-immune condition and usually occurs within 48-72 hrs post commencing heparin
- PLT rarely < 100. PLT return to normal over 4 days
- There is no ↑ risk of thromboembolism.
- **Treatment**: continue the LMWH ttt and observe

### Type II HIT:

- It is much rarer, and also known as HIT with thrombosis, and usually occurs 5-10 days after starting heparin,
- PLT usually < 100 to about 50.
- Pt. is at ↑ risk of thromboembolic events.
- **Treatment**: Heparin products should be stopped and the patient commenced on alternative medication.

## Diagnosis (is clinical):

- PLT < 100 or < 50% of from the patient's baseline.
- **4T SCORE : LOW SCORE EXCLUDE HIT BETTER THAN HIGH SCORE TO CONFIRM HIT.**
- Exclude other causes of thrombocytopenia.

- Resolution of thrombocytopenia after cessation of heparin.
- Supportive lab test: **HIT Abs (Anti-heparin platelet factor 4 (PF4 IgG) antibodies)** BY ELISA using functional assay test (more specific) and immunoassays.

**Functional tests:** which measure PLT activity in the presence of the patient's serum and heparin, it includes:

- Heparin Induced Platelet Aggregation (HIPA).
- Serotonin Release Assay (SRA).

**Treatment: LABEL THE PATIENT AS ALLERGIC TO HEPARIN**

- **Stop** all forms of heparin and perform doppler ultrasound of lower limbs.
- **Follow platelet count daily.**
- **When platelet count return to normal , transition anticoagulation to warfarin of fondaparinux, treat for 30 days for HIT OR 3-6 month for HITT(HEPARIN INDUCED THROMBOCYTOPENIA AND THROMBOSIS).**
- Options of **alternative anticoagulants** which do not react with HIT antibodies, such as lepirudin, danaparoid and Argatroban.
- The heparinoid **Danaparoid** (a combination of heparin and dermatan sulphate) appears to be the drug of choice for acute treatment and prophylaxis because of its low placental permeability especially in **pregnant** patient.
- Hirudin is a direct thrombin inhibitor that is approved for treatment of patients with HIT.
- Other direct thrombin inhibitors: Bivalirudin and Argatroban.
- **Hirudin** should only be used when there is either cross-reactivity with heparin-induced antibodies or cutaneous allergy against heparinoids.
- **Warfarin should NOT** be initiated for longer term protection from further events until substantial platelet count recovery has occurred.
- HIT patients who are switched to warfarin alone after the discontinuation of heparin may paradoxically have worsening thrombosis and develop venous limb gangrene and skin necrosis duo to transient drop of protein C level which is usually happening with the start of heparin treatment.

**EX:** A 28-year-old pregnant woman is being treated for a DVT with unfractionated heparin. A recent blood test shows low platelets 35 ×109/L (N= 150-400). The best course of action for this woman is >>> **Stop heparin** and alternative anticoagulation should be started **Danaparoid.**

**What is the best way to monitor rivaroxaban compliance?**
**>> Prothrombin time (PT)**

## Novel oral anticoagulants (NOACs)

The table below summaries the three NOACs: dabigatran, rivaroxaban and apixaban.

| | Dabigatran | Rivaroxaban | Apixaban |
|---|---|---|---|
| **UK brand name** | **Pradaxa** | **Xarelto** | **Eliquis** |
| **Mechanism of action** | **Direct thrombin inhibitor** | **Direct factor Xa inhibitor** | Direct factor Xa inhibitor |
| **Route** | Oral | Oral | Oral |
| **Excretion** | Majority renal | Majority liver | Majority faecal |
| **NICE indications** | Prevention of VTE following hip/knee surgery<br><br>Treatment of DVT and PE<br><br>Prevention of stroke in non-valvular AF* | Prevention of VTE following hip/knee surgery<br><br>Treatment of DVT and PE<br><br>Prevention of stroke in non-valvular AF* | Prevention of VTE following hip/knee surgery<br><br>Treatment of DVT and PE<br><br>Prevention of stroke in non-valvular AF* |

NICE stipulate that certain other risk factors should be present. These are complicated and differ between the NOACs but generally require one of the following to be present:

- prior stroke or transient ischaemic attack
- age 75 years or older
- hypertension
- diabetes mellitus
- heart failure

| | Dabigatran | Rivaroxaban | Apixaban |
|---|---|---|---|
| **Mechanism of action** | **Direct thrombin inhibitor** | **Direct factor Xa inhibitor** | Direct factor Xa inhibitor |
| **Route** | Oral | Oral | Oral |
| **Excretion** | Majority renal | Majority liver | Majority faecal |

# Warfarin

Warfarin is an oral anticoagulant which inhibits the reduction of vitamin K to its active hydroquinone form, which in turn acts as a cofactor in the carboxylation of vitamin K dependent clotting factor **II**, **VII**, **IX** and **X** (mnemonic = **1972**) and **protein C**.

**Warfarin >>> Inhibition of vitamin K epoxide reductase enzyme,** which is an enzyme that converts vitamin K to its active form (hydroquinone).

## Indications:

- **Venous thromboembolism**: target INR = **2.5, (if recurrent 3.5)**
- **Atrial fibrillation**, target INR = 2.5
- **Mechanical heart valves**, target INR depends on the valve type and location. Mitral valves generally require a higher INR than aortic valves.

Patients on warfarin are monitored using the **INR** (international normalised ration), the ratio of the prothrombin time for the patient over the normal prothrombin time.

Warfarin has a long half-life and achieving a stable INR may take several days. There a variety of loading regimes and computer software is now often used to alter the dose.

## Factors that may potentiate warfarin (i.e. ↑ INR):

- **Liver** disease.
- P450 enzyme **inhibitors**, e.g.: amiodarone, ciprofloxacin >> ↑ **INR.**
- Drugs which displace warfarin from plasma albumin, e.g. **NSAIDs.**
- Inhibit platelet function: NSAIDs
- **Cranberry juice** (عصير التوت البرى)
- **Antibiotics** that kill intestinal flora >> ↓ Vit K absorption >> ↑ **INR.**
- **Metronidazole** and **co-trimoxazole** inhibit the clearance of the active S isomer of warfarin, therefore enhancing its anticoagulant effect.

**Clopidogrel** does not appear to have a clinically relevant effect on the pharmacokinetics or pharmacodynamics of warfarin. However, the concurrent use with warfarin, increases the bleeding risk.

## Side-effects:

- Hemorrhage
- **Teratogenic**, although can be **used in breast-feeding mothers**

- **Skin necrosis**: when warfarin is first started biosynthesis of protein C is reduced. This results in a **temporary procoagulant state** after initially starting warfarin, **normally avoided by concurrent heparin administration.** Thrombosis may occur in venules leading to skin necrosis.
- Purple toes

**Dentistry** in **warfarinised** patients >>> **check INR 72 hours before** procedure, **proceed if INR < 4.0**

The BNF gives specific advice with regards to this, in the section 'Prescribing in dental practice'. If a patient has a history of an **unstable INR** then it should be **checked within 24 hours of the dental procedure.**

Warfarin is teratogenic and should be stopped before the 6$^{th}$ week of pregnancy to minimise the risk of fetal abnormalities.

So any female on warfarin and ask for conception and pregnancy >>> **either** stop warfarin immediately and replace with LMWH (the ideal solution) **or** continue warfarin but change to LMWH within 6 weeks of conception (the more practical solution because less good compliance with injections of LMWH).

**EX**: A 60-year-old female with a mitral valve replacement (MVR) and (AF) on warfarin is due for extensive abdominal surgery.

What is the most appropriate therapy as regards her anticoagulation >>> **Stop warfarin 5 days pre-operatively, bridge therapy with LMWH** and give **vitamin K if INR is still above 3.0 on eve of operation.**

The most appropriate bridging therapy in this case is LMWH, with the last dose being given **not less than 24 hours prior to the procedure**, the warfarin having been discontinued five days prior to the procedure.

**NB**: **Warfarin should never be given alone, without heparin**, when starting for treating a thrombotic event. This is because when warfarin is started, there is a **pro-thrombotic state** created, by **falling protein C and protein S** (these are **vitamin K dependent natural anticoagulants**) and these fall **before** factors II, VII, IX and X.

## Warfarin overdose

| Disorder | Prothrombin time | APTT | Bleeding time | Platelet count |
|---|---|---|---|---|
| Warfarin administration | Prolonged | Normal | Normal | Normal |
| Aspirin administration | Normal | Normal | Prolonged | Normal |
| Heparin | Often normal (may be prolonged) | Prolonged | Normal | Normal |
| DIC | Prolonged | Prolonged | Prolonged | Low |

An update of the BCSH (British Committee for Standards in Hematology) guidelines emphasized the preference of **prothrombin complex concentrate (PCC)** over FFP in major bleeding.

PCC is product of choice for **warfarin reversal** in the setting of **active bleeding** and a **markedly raised INR.**

**PCC** with Vit K is used if there is **major bleeding** corresponding to **1500-2000 ml** or **> 30%** of blood volume loss.

**PCC (factors II, VII, IX, and X) 30-50 units/kg.**

**If** PCC is **unavailable**, **FFP 15 mL/kg** can be given (but is less effective).

Vit K IV is **slower** in onset than other options of (PCC, FFP & Factor 7 VIIa) and also it may make the patient resistant to re-dosing with warfarin (**difficult re-warfarinization**) and at increased risk of thrombo-embolic events at a later stage, but in practice this is not a major problem.

**Vit K dosage is 1-5 mg oral or 5-10 mg IV.**

| | |
|---|---|
| **Major bleeding** | **1) Stop warfarin.**<br>**2) Give Vitamin K 5mg IVI.**<br>**3) PCC - but if it is not available so, FFP.** |
| **INR > 8.0**<br>**Minor bleeding** | Stop warfarin, restart when INR < 5.0<br>Give **intravenous** vitamin K 1-3mg<br>Repeat dose of vitamin K if INR still too high after 24 hours. |
| **INR > 8.0**<br>**No bleeding** | Stop warfarin, restart when INR < 5.0<br>Give vitamin K 1-5mg **by mouth**, using the IV preparation orally<br>Repeat dose of vitamin K if INR still too high after 24 hours |
| **INR 5.0-8.0**<br>**Minor bleeding** | Stop warfarin, restart when INR < 5.0<br>Give **intravenous** vitamin K 1-3mg |
| **INR 5.0-8.0**<br>**No bleeding** | Withhold (omit) 1 or 2 doses of warfarin, then review INR<br>Reduce subsequent maintenance dose |

As FFP can take time to defrost, **prothrombin complex concentrate (PCC)** should be considered in cases of intracranial hemorrhage. It is used in such an urgent situation. The use of PCC is currently limited by availability.

**EX:** Pt with AF on warfarin, presented with DCL and intracranial hemorrhage. The most appropriate management is >> **Vit K IV + (PCC).**

Due to his warfarin therapy, he will have reduced levels of factors II, VII, IX and X and requires **replacement** to correct his INR rapidly. This is most effectively achieved by the administration of **prothrombin complex concentrate (PCC)** (Beriplex or **Octaplex ®**, 25-50 units/kg **IVI**).

These result in **complete reversal of the warfarin-induced anticoagulation within 10 minutes** but the clotting factors have a finite half-life and therefore **5 mg IV vitamin K** should be given at the same time.

Vit K will start to affect the INR within 4-8 hours.

PCC is plasma derived, so there is a potential risk of transfusion-transmitted infection and it is prothrombotic.

Fresh frozen plasma (**FFP**) contains more dilute clotting factors and therefore produces **inferior** correction and should **not** be used in the management of life-threatening bleeding (unless PCC is not available).

FFP contains low level of coagulation factors and it is estimated that even at a dose of 15 ml/kg, level of most factors will only approach 20% of normal.

**FFP** may **not completely reverse the effects of warfarin** so is **NOT recommended in many local guidelines.**

Cryoprecipitate and oral vitamin K are not recommended for the management of life-threatening bleeding.

Cryoprecipitate, recombinant factor VII and platelets are not indicated for warfarin reversal.

The rate of fatal hemorrhage in patients receiving warfarin approaches 1%.

**EX:** A 70-yrs-old male is admitted with **hematemesis**. He is currently being treated with warfarin for AF and his **INR is 10**. What is the most appropriate immediate treatment of his INR >> **Prothrombin complex concentrate (PCC).**

## Dabigatran

### Stop dabigatran two days before polypectomy

- **Mode of action:** Dabigatran is a **direct thrombin inhibitor** with a rapid onset of action.
- **It is administered as a prodrug**
  - The prodrug dabigatran etexilate is rapidly converted by tissue esterases to dabigatran.
- it is predominately (80%) excreted by the kidneys.
- The anticoagulant effect starts within minutes of oral ingestion and peaks after 2-3 hours.
- **Advantage of dabigatran:**
  - due to its short half-life, a patient's coagulation status will normalize more rapidly than that of a patient treated with warfarin in almost all cases.
  - No need for routine monitoring
- **Disadvantage of dabigatran**
  - **Dabigatran is not recommended in patients with prosthetic heart valves** because their safety and efficacy have not established.
    - The rates of thromboembolism are higher for valves in the mitral compared with those in the aortic position.
    - **caged-ball valves are the most thrombogenic** followed by tilting-disk and bi-leaflet valves.
  - more thromboembolic events (e.g., valve thrombosis, stroke, TIA, and myocardial infarction) were observed with dabigatran than

with warfarin;
  - excessive major bleeding (predominantly postoperative pericardial effusions requiring intervention for hemodynamic compromise) was observed with dabigatran, compared with warfarin.
- **Monitoring of the anticoagulant effects of dabigatran**
  - In general, "routine" monitoring is not required in most cases.
  - However, in some clinical situations a clinician may wish to determine the degree to which dabigatran is reducing the coagulant potential of the blood; e.g., if a patient taking dabigatran requires emergency surgery, has an intracranial or major systemic bleed, or is being considered for thrombolysis due to an ischemic stroke.
  - **The thrombin time (TT) and ecarin clotting time are considered the most accurate measures of dabigatran's anticoagulant effect.**
    - The aPTT and, if available, the thrombin time (TT) should be used to measure the anticoagulant effect of dabigatran,
  - INR and PT tests are unreliable
- **Effect of dabigatran on procedural bleeding risk**
  - **Dabigatran should be discontinued 1 to 2 days (creatinine clearance ≥ 50 mL/min)** or 3 to 5 days (creatinine clearance <50 mL/min) before invasive or surgical procedures.
  - Clinicians may want to consider "longer" periods of discontinuation for patients undergoing major surgery in which bleeding could have serious consequences (e.g., cardiac, neurosurgery, major abdominal or pelvic, spinal puncture, or placement of a spinal or epidural catheter or port).
  - If surgery is urgent and cannot be delayed, there is an increased risk of bleeding; **patients with a normal aPTT appear to have a low risk of serious bleeding.**
- **conversion from warfarin to dabigatran** (eg: patient had difficulty attending for regular INR)
  - **if a patient is taking warfarin with a therapeutic INR, it is recommended to: Stop warfarin, perform daily INR, start dabigatran when INR falls below 2.0**
  - The anticoagulant effect of dabigatran starts minutes after its oral administration and peaks after 2-3 hours.
- **Contraindications**
  - **Dabigatran is contraindicated if eGFR <30ml/min.**
  - **Rivaroxaban, a direct inhibitor of activated factor X, is contraindicated if eGFR <15 and needs dose adjustment if eGFR 15–29 mL/minute.**

**Ecarin clotting time is prolonged by direct thrombin inhibitors such as dabigatran.**

**Treatment with aspirin, warfarin or heparins does not affect Ecarin clotting time.**

**Idarucizumab reverses dabigatran**

## Busulfan

- alkylating antineoplastic agent,
- Busulfan was the mainstay of the chemotherapeutic treatment of chronic myeloid leukemia (CML) until it was displaced by the new gold standard, imatinib
- Busulfan is used in pediatrics and adults in combination with cyclophosphamide or fludarabine/clofarabine as a conditioning agent prior to bone marrow transplantation, especially in chronic myelogenous leukemia (CML) and other leukemias, lymphomas, and myeloproliferative disorders.
- **Busulfan lung**
  - **Busulfan lung is a form of drug-induced pulmonary toxicity with an idiopathic pulmonary fibrosis-like picture.**
  - It is clinically symptomatic in 5% of patients.
  - There are no predictors of toxicity and pulmonary function testing is not a useful "screening" test.
  - Withdrawal of busulfan is the key step in treatment.

## Vinblastine

- Vinblastine is an **M phase**-specific chemotherapeutic agent that works by **disrupting the assembly of microtubules via binding tubulin.**
- Cell death results because anaphase cannot commence without the formation of the mitotic spindle and kinetochore.
- **Which cellular event occurs in the same phase of the cell cycle at which vinblastine functions? >> Breakdown of the nuclear membrane**
- **Breakdown of the nuclear membrane** occurs during the prometaphase portion of mitosis.

**Taxanes (e.g. Docetaxel) prevent microtubule disassembly**

# Cisplatin

**Cisplatin may cause peripheral neuropathy**

**Cisplatin is associated with hypomagnesaemia**

**Platin**um-based antineoplastic (end with: -**platin**)

## Mechanism of action

- **Causes crosslinking in DNA >>** makes it impossible for rapidly dividing cells to duplicate their DNA for mitosis.

## Side effects

- Marrow toxicity
- **Ototoxicity**
  - Due to vestibulocochlear nerve **damage (CNVIII)**
  - Sodium Thiosulfate Prevents Cisplatin-Induced Hearing Loss in Children With Cancer
- Peripheral neuropathy
- Nephrotoxicity
  - The nephrotoxicity of platinum-class drugs seems to be related to reactive oxygen species
  - Hypocalcaemia, **hypomagnesaemia** and hypokalaemia may occur as a result of nephrotoxicity
  - Amifostine is an antidote for cisplatin treatment to counteract nephrotoxicity.
  - Adequate hydration and diuresis is used to prevent renal damage.
    - ➢ Chloride diuresis is a renal procedure that can be performed to prevent the nephrotoxicity caused by cisplatin.
- Alopecia,
- Changes in taste.
- Although optic neuritis is described it is not a typical side effect.

# Trastuzumab

**Trastuzumab (Herceptin) - cardiac toxicity is common**

A baseline echocardiogram to assess heart function is recommended prior to starting trastuzumab.

- Trastuzumab (Herceptin) is a monoclonal antibody directed against the HER2/neu receptor.
- It is used mainly in metastatic breast cancer although some patients with early disease are now also given trastuzumab.

## Adverse effects

- flu-like symptoms and diarrhoea are common
- **cardiotoxicity: associated with Dilated cardiomyopathy** in 2% to 7% of users
  - more common when anthracyclines have also been used(eg : **Doxorubicin**).
  - Toxic to cardiac muscle itself with relative sparing of the electrical conductivity of the heart
  - Studies have shown that activation of **Erb-b2** (also known as HER-2), the receptor blocked by trastuzumab (Herceptin), is important in preventing the development of cardiomyopathy
  - Mechanism
    - Anthracyclines >> activate stress signal pathways within the heart >> cardiac damage
    - HER2 activation is protective against the damage that this stress signaling induces
    - HER2 inhibition removes this layer of protection, leading to >> dilated cardiomyopathy.
  - An echo is usually performed before starting treatment
  - **Regular echocardiogram (three monthly) is the best test to assess treatment safety**
  - Reduction of greater than 10% in ejection fraction indicating the need to stop treatment.

**In which chemotherapeutic agents is the cumulative dose limited due to cardiotoxicity?**

- **anthracycline chemotherapeutic agents** (eg: Epirubicin)
  - Epirubicin and the other anthracycline chemotherapeutic agents are extremely potent but are **limited by dose constraints**.
  - Cumulative doses of over 900 mg/m2 can lead to significant cardiac toxicity and heart failure.
  - Trastuzumab can cause direct myocardial damage and must be monitored with regular echocardiograms but it is not limited to a maximum lifetime dose.

## Imatinib

- **Belong to the class of >> Signal transduction inhibitor**
- Imatinib is a **tyrosine kinase inhibitor** which is fairly specific for the bcr/abl protein. It blocks the active site, which has a number of downstream effects.
  - The result is reduced cell proliferation, reduced cell motility, decreased adhesion and increased apoptosis.
- **Indications**
  - accelerated or blast crisis phase of CML.
  - gastrointestinal stromal tumours.

## Tamoxifen

Tamoxifen is a selective estrogen receptor modulator (SERM) which acts as an oestrogen receptor antagonist and partial agonist.
It is used in the management of oestrogen receptor positive breast cancer

### Adverse effects

- menstrual disturbance: vaginal bleeding, amenorrhoea
- hot flushes
- venous thromboembolism
  - **Particularly during and immediately after major surgery or periods of immobility**
- endometrial cancer

Tamoxifen is typically used for 5 years following removal of the tumour.
Raloxifene is a pure oestrogen receptor antagonist, and carries a lower risk of endometrial cancer

## UK licensed monoclonal antibodies

| Name | Target | Licensed indication |
|---|---|---|
| **Infliximab** | TNF-α | Refractory Crohn's, Crohn's fistulas, refractory rheumatoid arthritis |
| **Palivizumab** | F protein on RSV | Prophylaxis, RSV in premature infants or brochopulmonary dysplasia |
| **Abciximab** | Platelet glycoprotein IIb/IIIa | High risk coronary intervention |
| **Rituximab** | CD20 | Refractory low grade or follicular B cell lymphoma |
| **Basiliximab** | IL-2 receptor α chain | Prophylaxis of acute rejection in allogeneic renal transplantation |
| **Daclizumab** | IL-2 receptor α | As Basiliximab |
| **Trastuzumab** | HER 2 growth receptor | Relapsed HER2 (high) breast malignancy |

IL-2, interleukin 2; TNF-α, tumour necrosis factor α; RSV, respiratory syncitial virus.

## Rituximab

- **Rituximab binds to CD20,** an antigen located on pre-B and mature B-lymphocytes
- The receptor is thought to mediate B-cell lysis and apoptosis
- After rituximab therapy, levels of B-lymphocytes appear suppressed for around 6 months, with levels slowly increasing after this time
- As well as for rheumatoid arthritis, rituximab is **also used for the treatment of non-Hodgkin's lymphoma**
- Infusion reactions associated with cytokine release occur in up to 15% of patients receiving rituximab, and the medicine is administered in a specialist centre for this reason

# Monoclonal antibodies

Monoclonal antibodies have an increasing role in medicine.

They are manufactured by a technique called somatic cell hybridization.

This involves the fusion of myeloma cells with spleen cells from a mouse that has been immunized with the desired antigen. The resulting fused cells are termed a **hybridoma** and act as a 'factory' for producing monoclonal antibodies.

The main limitation to this is that mouse antibodies are immunogenic leading to the formation of human anti-mouse antibodies (HAMAs). This problem is overcome by combining the **variable region** from the **mouse** body with the **constant region** from **a human antibody**.

## Clinical examples of monoclonal antibodies:

- **Infliximab (anti-TNF)**: used in RA and Crohn's.
- **Rituximab (anti-CD20)**: used in **RA** and **non-Hodgkin's lymphoma**.
- **Cetuximab (Epidermal growth factor receptor antagonist)**: used in metastatic colorectal cancer and head and neck cancer.
- **Abciximab (glycoprotein IIb/IIIa receptor antagonist)**: prevention of ischaemic events in patients undergoing PCI.
- Trastuzumab (Herceptin) **(HER2/neu receptor antagonist)**: used in metastatic breast cancer. >> side effect: **Cardiotoxicity (DCM)** more common when **anthracyclines** have also been used.>> so an **echo** is usually performed **before** starting treatment
- **Alemtuzumab** (anti-CD52): used in **chronic lymphocytic leukemia**.
- OKT3 (anti-CD3): used to prevent organ rejection

## Monoclonal antibodies are also used for:

- Medical imaging when combined with a radioisotope.
- Identification of cell surface markers in biopsied tissue.
- Diagnosis of viral infections.

# Anti-oestrogen drugs

## Selective oEstrogen Receptor Modulators (SERM)

Tamoxifen is a SERM which acts as an oestrogen receptor antagonist and partial agonist. It is used in the management of oestrogen receptor-positive breast cancer.

### Adverse effects

- menstrual disturbance: vaginal bleeding, amenorrhoea
- hot flushes - 3% of patients stop taking tamoxifen due to climacteric side-effects
- venous thromboembolism
- endometrial cancer

## Aromatase inhibitors

Anastrozole and letrozole are **aromatase inhibitors that reduces peripheral oestrogen synthesis.** This is important as aromatisation accounts for the majority of oestrogen production in postmenopausal women and therefore anastrozole is used for ER +ve breast cancer in this group.

### Adverse effects

- **osteoporosis**
  - NICE recommends a DEXA scan when initiating a patient on aromatase inhibitors for breast cancer
- hot flushes
- arthralgia, myalgia
- insomnia

# Cyclophosphamide

Cyclophosphamide is an **alkylating agent** used in the management of cancer and autoimmune conditions. It works by causing cross-linking of DNA

## Adverse effects

- **haemorrhagic cystitis:** incidence reduced by the use of hydration and **mesna**
- **myelosuppression**
- transitional cell carcinoma

## Mesna

- 2-mercaptoethane sulfonate Na
- a metabolite of cyclophosphamide called acrolein is toxic to urothelium
- mesna binds to and inactivates acrolein helping to prevent haemorrhagic cystitis

# Lead poisoning

Along with acute intermittent porphyria, lead poisoning should be considered in questions giving a combination of abdominal pain and neurological signs. Lead poisoning results in defective ferrochelatase and ALA dehydratase function.

## Features

- **abdominal pain**
- **peripheral neuropathy (mainly motor)**
- fatigue
- constipation
- **blue lines on gum** margin (only 20% of adult patients, very rare in children)

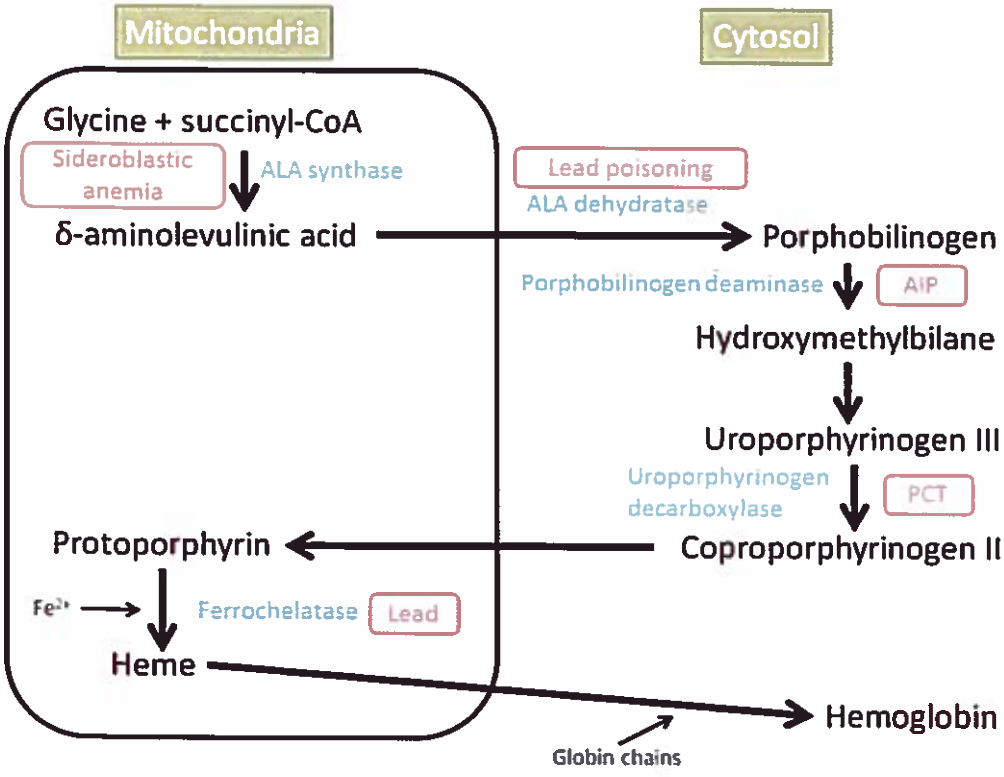
## Investigations

- the blood lead level is usually used for diagnosis. Levels greater than 10 mcg/dl are considered significant
- full blood count: microcytic anaemia. Blood film shows red cell abnormalities including **basophilic stippling** and clover-leaf morphology
- raised serum and urine levels of delta aminolaevulinic acid may be seen making it sometimes difficult to differentiate from acute intermittent porphyria
- urinary coproporphyrin is also increased (urinary porphobilinogen and uroporphyrin levels are normal to slightly increased)
- in children, lead can accumulate in the metaphysis of the bones although x-rays are not part of the standard work-up

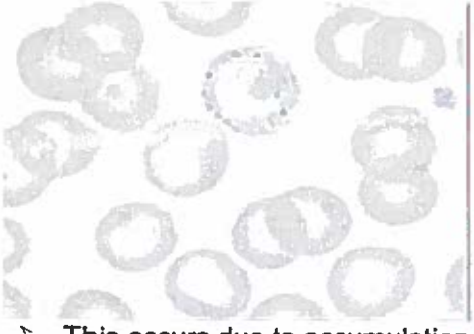
**Management** - various chelating agents are currently used:

- dimercaptosuccinic acid (DMSA)
- D-penicillamine
- EDTA

Dimercaprol




**Blood film shows basophilic (blue) stippling of the RBCs in Lead poisoning & Thalassemia**



- This occurs due to accumulation of ribonucleic acid (RNA) in the RBCs due to inhibition of pyrimidine 5 nucleotidase by lead. The denatured RNA is revealed as basophilic stippling.
- Other features include mild anaemia, encephalopathy and peripheral motor neuronopathies
- Patients with learning disabilities may be prone to lead poisoning due to pica.
- Basophilic stippling: seen in Lead poisoning & Thalassaemia

# Cytotoxic agents

The tables below summarises the mechanism of action and major adverse effects of commonly used cytotoxic agents.

## Alkylating agents:

| Cytotoxic | Mechanism of action | Adverse effects |
|---|---|---|
| **Cyclophosphamide** | Alkylating agent - causes cross-linking in DNA. | • **Haemorrhagic cystitis: (Incidence reduced by the use of hydration and mesna),**<br>• **Transitional cell carcinoma.**<br>• **Myelosuppression.** |

## Cytotoxic antibiotics:

| Cytotoxic | Mechanism of action | Adverse effects |
|---|---|---|
| **Bleomycin** | Degrades preformed DNA. | **Lung fibrosis** |
| **Doxorubicin** | Stabilizes DNA-topoisomerase II complex. Inhibits DNA & RNA synthesis. | **Cardiomyopathy (DCM)** |

## Antimetabolites:

| Cytotoxic | Mechanism of action | Adverse effects |
|---|---|---|
| **Methotrexate** | Inhibits dihydrofolate reductase and thymidylate synthesis. | Myelosuppression, mucositis, liver fibrosis, lung fibrosis |
| Fluorouracil (5-FU) | Pyrimidine analogue inducing cell cycle arrest and apoptosis by blocking thymidylate synthase (works during S phase) | Myelosuppression, diarrhoea, mucositis, dermatitis |
| 6-mercaptopurine | Purine analogue that is activated by HGPRTase, decreasing purine synthesis | Myelosuppression |
| Cytarabine | Pyrimidine antagonist. Interferes with DNA synthesis specifically at the S-phase of the cell cycle and inhibits DNA polymerase | Myelosuppression, ataxia |

NB: **Capecitabine** is an **orally** administered **prodrug** which is enzymatically converted to 5-fluorouracil (5FU) in the tumour.

## Acts on microtubules:

| Cytotoxic | Mechanism of action | Adverse effects |
|---|---|---|
| **Vincristine**, Vinblastine | Inhibits formation of microtubules, **mitosis** inhibitor (**M** stage of cell cycle) | **Vincristine: Peripheral neuropathy** (reversible), paralytic ileus (UB atony, hesitancy). Vinblastine: myelosuppression |
| **Docetaxel (Taxanes)** | **Prevents microtubule depolymerization** & **disassembly,** decreasing free tubulin. | Neutropenia, peripheral neuropathy |

## Other cytotoxic drugs:

| Cytotoxic | Mechanism of action | Adverse effects |
|---|---|---|
| **Cisplatin** | Causes **cross-linking in DNA** | **Ototoxicity, Peripheral neuropathy, Hypomagnesaemia** |
| Hydroxyurea (hydroxycarbamide) | Inhibits ribonucleotide reductase, decreasing DNA synthesis | Myelosuppression |

**EX:** A 60-year-old man who is currently receiving chemotherapy for non-small cell lung cancer presents for review. He is currently being treated with oral calcium supplements as hypocalcaemia was detected during a recent admission. Which one test may help determine why his **calcium level remains low despite calcium supplementation >> serum Magnesium >>> Cisplatin**, often used in the management of **non-small cell lung cancer**, is a well-known cause of **magnesium deficiency**. Without **first correcting magnesium levels it is difficult to reverse hypocalcaemia**. Whilst measuring the parathyroid hormone level is always useful it is likely to be elevated unless the patient has coexistent hypoparathyroidism.

**5-FU:**

**Dihydropyrimidine dehydrogenase (DPD)** is the enzyme responsible for the breakdown of 5-FU. A **pharmacogenetic** disorder has been described concerning cancer patients with a **complete or partial deficiency of DPD**. In this they suffer **severe toxicity**, like new onset florid **diarrhoea, severe oral mucositis** and even including **death**, following the administration of 5-FU. It is similar to the picture seen with an overdose of 5-FU and is recognized in approximately 3% of patients.

## Interferons (IFN)

Interferons (IFN) are cytokines released by the body in response to viral infections and neoplasia.
They are classified according to cellular origin and the type of receptor they bind to.
IFN-alpha and IFN-beta bind to type 1 receptors whilst IFN-gamma binds only to type 2 receptors.
**IFN-alpha** is produced by leucocytes and has an antiviral action. It has been shown to be useful in the management of:

- **Hepatitis B & C,**
- **Kaposi's sarcoma,**
- **Metastatic renal cell cancer,**
- **Polycythaemia rubra vera,**
- **CML**
- **Hairy cell leukaemia.**

### Side effects of IFN-alpha:

- Flu like symptoms
- Depression
- Neutropenia → immunosuppression
- Erythema, pain, hardness on the spot of injection

## Hormone replacement therapy (HRT): adverse effects

HRT involves the use of a small dose of estrogen **(combined with a progestogen in women with a uterus)** to help alleviate menopausal symptoms.

### Side-effects:

- Nausea
- Breast tenderness
- Fluid retention and weight gain

### Potential complications:

- Increased risk of **breast cancer**: increased by the addition of a progestogen.
- Increased risk of **endometrial cancer**: **reduced** by the addition of a **progestogen** but not eliminated completely. The BNF states that the additional risk is eliminated if a progestogen is given continuously.
- Increased risk of **venous thromboembolism**: increased by the addition of a progestogen.

- Increased risk of **cerebrovascular stroke.** (BNF states that the stroke risk is the same regardless of whether the HRT preparation contains progesterone or oestrogen only).
- Increased risk of **ischaemic heart disease** if taken more than 10 years after menopause.

## Breast cancer:

- In the Women's Health Initiative (WHI) study there was a relative risk of 1.26 at 5 years of developing breast cancer
- The increased risk relates to duration of use
- The breast cancer incidence is higher in women using combined preparations compared to estrogen-only preparations
- The risk of breast cancer begins to decline when HRT is stopped and by 5 years it reaches the same level as in women who have never taken HRT.
- **This is the rationale behind giving women who've had a hysterectomy oestrogen-only treatment.**

**EX:** Old woman who has **had a hysterectomy** presents for advice about **HRT**. Which one of the following would result from the use of a **combined** oestrogen-progestogen preparation compared to an oestrogen-only preparation >> ↑ **Increased risk of breast cancer**

**Ewing's sarcoma:**
It is the **most lethal malignant primary** bone tumour derived from the red bone marrow.
It is most common in **children and adolescents** and rare after the age of 30 years.
It has a **male**: female ratio about 3:2.
The earliest symptom is **pain**, which is usually **intermittent** but becomes increasingly intense.
Delay in the diagnosis can occur due to the fact that the clinical picture may **be similar to that of acute or chronic osteomyelitis**. However, eventually most patients have a **large palpable rapidly growing mass**, which is tense and tender.
Associations with a poor prognosis include the **male** sex, **age > 12 years**, ↑ **elevated LDH**, **anaemia** and a poor response to chemotherapy.

## Extravasation of the chemotherapeutic agents:

- **Stop the infusion**, **immobilize** the arm and attempt to **aspirate** any accessible drug from the cannula and extravasation site before removal of the cannula.
- Agent specific **antidote** can be used after specialist advice.

- **Cold compresses** are generally applied except in the case of **vinca alkaloids** in which case a **heat** compress should be applied.
- Doxorubicin and Daunorubicin extravasation injuries are particularly prone to causing ulceration and so **plastic surgery** opinion is needed.
- Consider **reporting** to National Extravasation Information Service.

# Allergies

## Allergy tests

| | |
|---|---|
| **Skin prick test** | • **Most commonly used test as an easy to perform and inexpensive.**<br>• **the first line for detection of allergen-specific IgE**<br>• **Drops of diluted allergen are placed on the skin after which the skin is pierced using a needle.**<br>• **A large number of allergens can be tested in one session.**<br>• **Normally includes a histamine (positive) and sterile water (negative) control.**<br>• **A wheal will typically develop if a patient has an allergy.**<br>• **Can be interpreted after 15 minutes**<br>• **Useful for food allergies and also pollen**<br>• **It can induce anaphylaxis, and must therefore be done in an environment where resuscitation facilities are available.** |
| **Radioallergosorbent test (RAST)** | • Determines the amount of IgE that reacts specifically with suspected or known allergens, for example IgE to egg protein.<br>• Results are given in grades from 0 (negative) to 6 (strongly positive)<br>• Useful for food allergies, inhaled allergens (e.g. Pollen) and wasp/bee venom<br>• Blood tests may be **used when skin prick tests are not suitable, for example if there is extensive eczema or if the patient is taking antihistamines** |
| **Skin patch testing** | • **Useful for contact dermatitis.**<br>• Around 30-40 allergens are placed on the back.<br>• Irritants may also be tested for.<br>• The patches are **removed 48 hours later** with the results being read by a dermatologist after a further 48 hours |

# Anaphylaxis

Anaphylaxis may be defined as a severe, life-threatening, generalised or systemic hypersensitivity reaction.

### Common identified causes of anaphylaxis:

- food (e.g., nuts) - the most common cause in children
- drugs
- venom (e.g., wasp sting)

## Features

### The Resus Council UK define anaphylaxis as:

- the sudden onset and rapid progression of symptoms
- Airway and/or Breathing and/or Circulation problems

### Airway problems may include:

- swelling of the throat and tongue →hoarse voice and stridor

### Breathing problems may include:

- respiratory wheeze
- dyspnoea

### Circulation problems may include:

- hypotension
- tachycardia

This means that if there are no ABC problems then the patient is technically not having anaphylaxis.

### Around 80-90% of patients also have skin and mucosal changes:

- generalised pruritus
- widespread erythematous or urticarial rash

## Management

Anaphylaxis is one of the few times when you would not have time to look up the dose of a medication.

The Resuscitation Council guidelines on anaphylaxis have recently been updated.

**Intramuscular adrenaline** is by far the most important drug in anaphylaxis and should be given as soon as possible.

Previously IV hydrocortisone was also recommended but the evidence base for this was poor and it was removed in the 2021 update.

The recommended doses for adrenaline are as follows:

| Age | Adrenaline dose |
|---|---|
| **< 6 months** | 100 - 150 micrograms (0.1 - 0.15 ml 1 in 1,000) |
| **6 months - 6 years** | 150 micrograms (0.15 ml 1 in 1,000) |
| **6-12 years** | 300 micrograms (0.3ml 1 in 1,000) |
| **Adult and child > 12 years** | 500 micrograms (0.5ml 1 in 1,000) |

Adrenaline can be repeated every 5 minutes if necessary. The best site for IM injection is the **anterolateral aspect of the middle third of the thigh**.

## Refractory anaphylaxis

- defined as respiratory and/or cardiovascular problems persist despite 2 doses of IM adrenaline
- IV fluids should be given for shock
- expert help should be sought for consideration of an IV adrenaline infusion

## Management following stabilization:

- non-sedating oral antihistamines, in preference to chlorphenamine, may be given following initial stabilisation especially in patients with persisting skin symptoms (urticaria and/or angioedema)
- sometimes it can be difficult to establish whether a patient had a true episode of anaphylaxis. Serum tryptase levels are sometimes taken in such patients as they remain elevated for up to 12 hours following an acute episode of anaphylaxis
- all patients with a new diagnosis of anaphylaxis should be referred to a specialist allergy clinic
- an adrenaline injector should be givens an interim measure before the specialist allergy assessment (unless the reaction was drug-induced)
- patients should be prescribed 2 adrenaline auto-injectors
- training should be provided on how to use it

a risk-stratified approach to discharge should be taken as **biphasic** reactions can occur in up to 20% of patients

**The Resus Council UK recommend the following risk-stratified approach to discharge:**

**fast-track discharge** (after 2 hours of symptom resolution):

- good response to a single dose of adrenaline
- complete resolution of symptoms
- has been given an adrenaline auto-injector and trained how to use it
- adequate supervision following discharge

**minimum 6 hours** after symptom resolution

- 2 doses of IM adrenaline needed, or
- previous biphasic reaction

**minimum 12 hours** after symptom resolution

- severe reaction requiring > 2 doses of IM adrenaline
- patient has severe asthma
- possibility of an ongoing reaction (e.g. slow-release medication)
- patient presents late at night

- patient in areas where access to emergency access care may be difficult
- observation for at 12 hours following symptom resolution

## Latex allergy

### Sensitivity to latex may cause a number of problems:

- type I hypersensitivity (anaphylaxis)
- type IV hypersensitivity (allergic contact dermatitis)
- irritant contact dermatitis

Latex allergy is more common in children with myelomeningocele spina bifida.

### Latex-fruit syndrome

It is recognized that many people who are allergic to latex are also allergic to fruits, particularly banana, pineapple, avocado, chestnut, kiwi fruit, mango, passion fruit and strawberry.

MRCPUK part-1 exam: **A nurse who is known to have an allergy to latex develops a widespread urticarial rash and facial oedema shortly after eating lunch. Which food is she most likely to have consumed?** Banana

## Oral allergy syndrome

Oral allergy syndrome, also known as pollen-food allergy, is an IgE-mediated hypersensitivity reaction to specific raw, plant-based foods including fruits, vegetables, nuts and certain spices.
It typically presents with mild tingling or pruritus of the lips, tongue and mouth.
This hypersensitivity reaction is initiated by cross-reaction with a non-food allergen, most commonly birch pollen whereby the protein in the food is similar but not identical in structure to the original allergen.
This explains why **OAS is strongly linked with pollen allergies and presents with seasonal variation.**
It also explains why cooking culprit food, and thereby denaturing the proteins, prevents symptoms occurring.

### OAS vs food allergies:

- A food allergy is caused by direct sensitivity to a protein present in food. OAS is caused by cross-sensitisation to a structurally similar allergen present in pollen.
- Non-plant foods do not cause OAS because there are no cross-reactive allergens in pollen which would be structurally similar to meat. Food allergies may be caused by plant or non-plant foods and

allergens occur in response to substances that are more stable and able to survive stomach enzymes and acid processing and cooking.
- Food allergies are more likely to cause systemic symptoms (vomiting and diarrhoea) and are more likely to lead to anaphylaxis because the allergens are not readily broken down. The symptoms of OAS are normally limited to the oropharynx because the proteins that cause the symptoms are denatured by stomach enzymes.

## Epidemiology:

- About 2% of the UK population has OAS but this is probably under-diagnosed.
- About 1/2 of patients with a general pollen allergy and 3/4 of patients with an allergy to birch pollen (the most common allergen in the UK) report symptoms of OAS.

## Associations:

- Birch pollen allergy (most common)
- Rye grass pollen allergy
- Rubber latex allergy

## Presentation:

- OAS should be suspected in patients with a history of seasonal allergy symptoms (rhinitis, conjunctivitis and asthma) who present with symptoms minutes after eating a specific raw food.
- **Itching and tingling of the lips, tongue and mouth are the most common symptoms**
- Mild swelling and redness of the lips, tongue and throat may occur.
- In severe cases, patients develop nausea and vomiting.
- Symptoms fully resolve within one hour of contact.
- Anaphylaxis is a very rare complication.

## Signs:

- Most patients will have no visible signs during or between episodes of OAS.
- Some patients may have visible swelling and redness of the lips, tongue and oral mucosa.
- Patients with anaphylaxis present with wheeze, hives, hypotension and collapse.

## Investigations:

- OAS is a clinical diagnosis but further tests can be used to rule out diagnoses such as food allergies and to confirm the diagnosis when the history is unclear.
- Standard IgE RAST and skin prick testing may be performed to identify common allergens such as pollens which co-exist with OAS. Note that

common pollen allergies have specific associated foods which cause OAS. For example, birch allergy is associated with sensitivity to, amongst others, carrot, parsley and spinach.
- Food-specific IgE testing: this is unreliable and rarely performed clinically because the food does not survive processing.
- Skin prick testing with culprit foods is more commonly used. *A positive test would cause a small, itchy lump to develop on the skin.*

### Management:
- Avoidance of culprit foods is the only required modification for the vast majority of patients.
- If culprit food is eaten and symptoms develop, an oral antihistamine can be taken.
- If symptoms of anaphylaxis develop, an ambulance should be called. Intramuscular adrenaline may be required.
- Patients should be informed that once cooked, culprit foods should not cause symptoms.

## Hereditary angioedema

Hereditary angioedema (HAE) is **an autosomal dominant** condition associated with low plasma levels of the C1 inhibitor (C1-INH, C1 esterase inhibitor) protein.
C1-INH is a multifunctional serine protease inhibitor - the probable mechanism behind attacks is uncontrolled release of bradykinin resulting in oedema of tissues.

### Investigation
- C1-INH level is low during an attack
- low C2 and C4 levels are seen, even between attacks. Serum C4 is the most reliable and widely used screening tool

### Symptoms
- attacks may be proceeded by painful macular rash
- painless, non-pruritic swelling of subcutaneous/submucosal tissues
- may affect upper airways, skin or abdominal organs (can occasionally present as abdominal pain due to visceral oedema)
- urticaria is not usually a feature

### Management
- **acute**
  - HAE does not respond to adrenaline, antihistamines, or glucocorticoids

- IV C1-inhibitor concentrate, fresh frozen plasma (FFP) if this is not available
- prophylaxis: anabolic steroid Danazol may help
- **low c4 common in:**
  - SLE
  - Cryoglobulinemia
  - Angiodema

## IgG4-related disease

IgG4-related disease has been described in virtually every organ system: the biliary tree, salivary glands, periorbital tissues, kidneys, lungs, lymph nodes, meninges, aorta, breast, prostate, thyroid, pericardium, and skin. The histopathological features are similar across organs, regardless of the site.
IgG4-related disease is analogous to sarcoidosis, in which diverse organ manifestations are linked by similar histopathological characteristics. Raised concentrations of IgG4 in tissue and serum can be helpful in diagnosing IgG4 disease, but neither is a specific diagnostic marker.

### Examples include:

- Riedel's Thyroiditis
- Autoimmune pancreatitis
- Mediastinal and Retroperitoneal Fibrosis
- Periaortitis/periarteritis/Inflammatory aortic aneurysm
- Kuttner's Tumour (submandibular glands) & Mikulicz Syndrome (salivary and lacrimal glands)
- Possibly sjogren's and primary biliary cirrhosis

## Post cranial irradiation somnolence syndrome (SS)

It was first identified in patients treated with radiotherapy for scalp ringworm infection

It is characterised by **excessive somnolence, lethargy** and **clumsiness** and tends to occur around **11-21** or **31-35 days** after high dose cranial radiotherapy.
**No focal cause** is identified and it is postulated that it may occur due to post irradiation **demyelination**.
**No specific therapy** is required, some case reports suggest that **corticosteroids** may be of use but the evidence is not firmly established.

## Chemotherapy side-effects: nausea and vomiting

- Nausea and vomiting are common side-effects of chemotherapy.
- Risk factors for the development of symptoms include:
  - anxiety
  - age less than 50 years old
  - concurrent use of opioids
  - the type of chemotherapy used
- For patients at low-risk of symptoms then drugs such as metoclopramide may be used first-line.
- For high-risk patients, then **5HT3 receptor antagonists such as ondansetron** are often effective, especially if combined with dexamethasone

## Adverse effects of other cancer treatment

### Purine analogue (eg: fludarabine) for CLL >> Pneumocyscis jirovecii infection

- This cytotoxic agent affects T-cell function. Patients are therefore prone to opportunistic infections including pneumocystis infection.
- Patients therefore receiving purine analogues should also receive co-trimoxazole to reduce this risk.
- All patients who receive purine analogues are at risk of **transfusion-associated graft-versus-host disease** and therefore should receive irradiated blood products. The clinical features of transfusion associated graft-versus-host disease are:
  - pancytopaenia,
  - liver dysfunction,
  - diarrhoea and
  - rash

### Etoposide >> secondary haematological malignancy

- In patients who have received Etoposide, secondary haematological malignancy may develop in as little as 1-3 years.
- It is currently indicated for the treatment of small cell lung cancer and non-seminomatous testicular carcinoma.

# Syringe drivers

A syringe driver should be considered in the palliative care setting when a patient is unable to take oral medication due to nausea, dysphagia, intestinal obstruction, weakness or coma.

**In the UK there are two main types of syringe driver:**

- Graseby MS16A (blue): the delivery rate is given in mm per hour
- Graseby MS26 (green): the delivery rate is given in mm per 24 hours

**The majority of drugs** are compatible with water for injection although for the following drugs sodium chloride 0.9% is recommended:

- granisetron
- ketamine
- ketorolac
- octreotide
- ondansetron

## Commonly used drugs

- nausea and vomiting: cyclizine, levomepromazine, haloperidol, metoclopramide
- respiratory secretions/bowel colic: hyoscine hydrobromide, hyoscine butylbromide, or glycopyrronium bromide.
- agitation/restlessness: midazolam, haloperidol, levomepromazine
- pain: diamorphine is the preferred opioid

## Mixing and compatibility issues

- diamorphine is compatible with the majority of other drugs used including dexamethasone, haloperidol, hyoscine butylbromide, hyoscine hydrobromide, levomepromazine, metoclopramide, midazolam
  - cyclizine may precipitate with diamorphine when given at higher doses
- cyclizine is incompatible with a number of drugs including clonidine, dexamethasone, hyoscine butylbromide (occasional), ketamine, ketorolac, metoclopramide, midazolam, octreotide, sodium chloride 0.9%

## Oncology in brief

### The most common causes of cancer in the UK are as follows*

- **Breast**
- **Lung**
- **Colorectal**
- Prostate
- Bladder
- Non-Hodgkin's lymphoma
- Melanoma
- Stomach
- Oesophagus
- Pancreas

### The most common causes of death from cancer in the UK are as follows:

- Lung
- Colorectal
- Breast
- Prostate
- Pancreas
- Oesophagus
- Stomach
- Bladder
- Non-Hodgkin's lymphoma
- Ovarian

*excludes non-melanoma skin cancer

**N.B:**
Between 5 and 10% of all breast cancers are thought to be hereditary. Mutation in the BRCA1 and BRCA2 genes also increase the risk of ovarian cancer.
For colorectal cancer around 5% of cases are caused by hereditary non-polyposis colorectal carcinoma (HNPCC) and 1% are due to familial adenomatous polyposis.
Women who have HNPCC also have a markedly increased risk for developing endometrial cancer - around 5% of endometrial cancers occur in women with this risk factor.

## Tumor markers

Tumor markers may be divided into:

- monoclonal antibodies against carbohydrate or glycoprotein tumour antigens
- tumour antigens
- enzymes (alkaline phosphatase, neurone specific enolase)
- hormones (e.g. calcitonin, ADH)

It should be noted that tumour markers usually have a low specificity

## Monoclonal antibodies

| Tumour marker | Association |
|---|---|
| CA 125 | Ovarian cancer |
| CA 19-9 | Pancreatic cancer |
| CA 15-3 | Breast cancer |

## Tumor antigens

| Tumour marker | Association |
|---|---|
| Prostate specific antigen (PSA) | Prostatic carcinoma |
| Alpha-feto protein (AFP) | Hepatocellular carcinoma, teratoma |
| Carcinoembryonic antigen (CEA) | Colorectal cancer |
| S-100 | Melanoma, schwannomas |
| Bombesin | Small cell lung carcinoma, gastric cancer, neuroblastoma |
| β-human chorionic gonadotrophin | choriocarcinomas, germ-cell tumours and lung cancers |

**Ex:** female pt. with ovarian mass with pleural effusion, ascites and ↑ CA 125 >>> **Meig's syndrome** = an ovarian fibroma assoc. with a pleural effusion and ascites.

**EX:** A 34-year-old man is reviewed four years after having an **Orchidectomy** for a **testicular teratoma**. What are the most useful follow-up investigations to detect disease recurrence? >> Alpha-fetoprotein + beta-HCG.

# Gingival hyperplasia

## Drug causes of gingival hyperplasia:

- **Phenytoin**
- **Cyclosporine**
- **CCB** (especially Nifedipine)

## Other causes of gingival hyperplasia include:

- **AML** (Acute myeloid leukaemia) (myelomonocytic and monocytic types)

## Thymoma

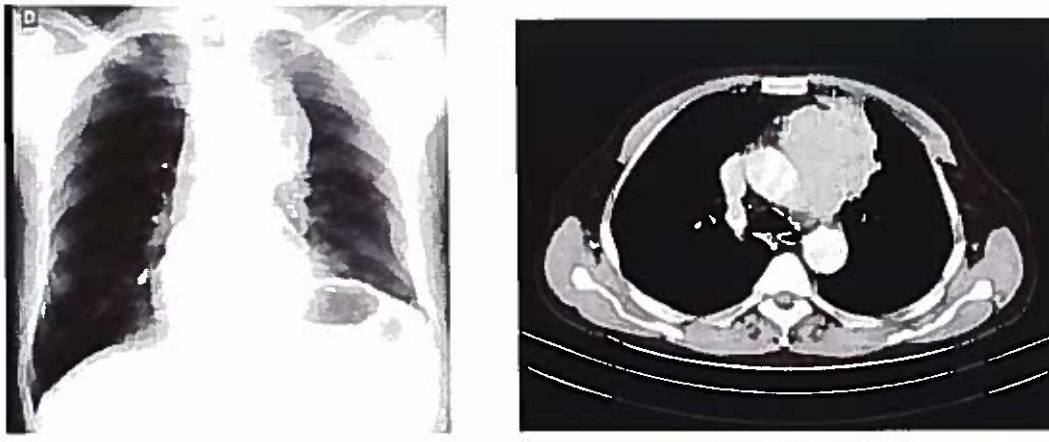
Thymomas are the most common tumour of the anterior mediastinum and is usually detected between the sixth and seventh decades of life.

### Associated with

- **Myasthenia gravis (30-40%** of patients with thymoma).
- **Red cell aplasia.**
- **Dermatomyositis**
- Also: SLE, **SIADH**

### Causes of death:

- Compression of airway
- cardiac tamponade



Cardiac tamponade Chest x-ray and accompanying CT scan of a patient with a thymoma. In the chest x-ray there is a partially delineated mediastinal mass (anterior mediastinum) with regular borders, bulging the left upper mediastinal contour

## Esophageal cancer

Until recent times oesophageal cancer was most commonly due to a squamous cell carcinoma but the incidence of adenocarcinoma is rising rapidly.

**Adenocarcinoma** is now the most common type of esophageal cancer and is more likely to develop in patients with a history of gastro-esophageal reflux disease (GORD) or Barrett's.

The majority of tumours are in **the middle third of the oesophagus**.

### Risk factors:

- Smoking
- Alcohol
- GORD
- Barrett's oesophagus
- Achalasia
- Plummer-Vinson syndrome
- Rare: coeliac disease, scleroderma

esophageal **adenocarcinoma** is associated with GORD or Barrett's.

Metaplastic columnar epithelium would be seen with Barrett's but this is not consistent with the obstructive lesion seen on endoscopy.

## Gastric cancer

### Epidemiology:

- Overall incidence is decreasing, but incidence of tumours arising from the cardia is increasing
- Peak age = 70-80 years
- More common in males, 2:1
- More common in Japan, China, Finland and Colombia than the West

### Associations:

- H. pylori infection
- Blood group **A**: g**A**stric c**A**ncer
- Gastric adenomatous polyps
- Pernicious anemia
- Smoking
- Diet: salty, spicy, nitrates
- May be negatively associated with duodenal ulcer

### Investigation:

- Diagnosis: endoscopy with biopsy
- Staging: CT or **endoscopic ultrasound (EUS)** - endoscopic ultrasound has recently been shown to be superior to CT

**N.B: Gastric adenocarcinoma** >> Biopsy shows: **Signet ring cells**

# Breast cancer

## Predisposing factors

- **BRCA1**, BRCA2 genes - 40% lifetime risk of breast/ovarian cancer
- 1st degree relative premenopausal relative with breast cancer (e.g. mother)
- **nulliparity,** 1st pregnancy > 30 yrs (twice risk of women having 1st child < 25 yrs)
- **early menarche, late menopause**
- **combined hormone replacement therapy** (relative risk increase * 1.023/year of use), **combined oral contraceptive use**
- past breast cancer
- not breastfeeding
- ionising radiation
- **p53 gene mutations**
- obesity
- previous surgery for benign disease (? more follow-up, scar hides lump)

# Paget's disease of the breast

## Overview

- Paget's disease of the breast is a rare (1-4% of breast cancers) form of breast cancer that affects the nipple and areola.
- underlying invasive breast cancer, or ductal carcinoma in situ (DCIS) almost always present
  - unlike Paget's disease of the vulva
- Malignant cells infiltrate into the epidermis via the mammary duct epithelium, leading to thickening of the affected skin.

## Features

- Presents with dermatitis or macular rash over nipple or areola
- It presents insidiously and is **similar in appearance to eczema**; as such it often goes undiagnosed for several months.

## Diagnosis

- **Skin biopsy with immunohistochemistry is the first line investigation.**
- Investigations should also be done for underlying malignancy:
  - biopsy if a lump is palpable,
  - imaging if no lump is palpable.

**Management:** usually surgical with post-operative radiotherapy

**Prognosis:** high chance of recurrence.

Paget's disease of the breast

## Colorectal cancer

### Overview:

- Colorectal cancer is the **third** most common cancer in the **UK**, with approximately 30,000 new cases in England and Wales per year.
- The lifetime risk of developing colorectal cancer in the United Kingdom is **5%.**
- Most cancers develop from adenomatous polyps.
- Screening for colorectal cancer has been shown to reduce mortality by 16%.
- The NHS now has a national screening programm offering screening every 2 years to all men and women aged 60 to 69 years. Patients aged over 70 years may request screening.
- Eligible patients are sent fecal occult blood (FOB) tests through the mail post.
- Patients with abnormal results are offered a colonoscopy.
- CEA (Carcinoembryonic antigen) may be used to monitor for recurrence in patients post-operatively or to assess response to treatment in patients with metastatic disease.

## At colonoscopy, approximately:

- 5 out of 10 patients will have a normal exam.
- 4 out of 10 patients will be found to have polyps which may be removed due to their premalignant potential.
- 1 out of 10 patients will be found to have cancer.

Colorectal cancer screening >>> PPV of FOB = **5 - 15%.**

**EX:** A 62-year-old man is called for review after a positive FOB test done as part of the national screening programme. During counselling for colonoscopy he asks what percentage of patients with a positive FOB test have colorectal cancer. What is the most accurate answer? >>> **5-15 %**

There is also a 30-45% chance of having an adenoma with a positive FOB test

# Cervical cancer

Human papilloma virus (HPV) infection is the most important risk factor for developing cervical cancer.
Subtypes 16,18 & 33 are particularly carcinogenic.
The other most common subtypes (6 & 11) are non-carcinogenic and associated with genital warts.

Infected endocervical cells may undergo changes resulting in the development of **koilocytes**.
**These have the following characteristics:**

- enlarged nucleus
- irregular nuclear membrane contour
- the nucleus stains darker than normal (hyperchromasia)
- a perinuclear halo may be seen

# Acute Tumor Lysis Syndrome (ATLS)

Tumor lysis syndrome occurs as a result of cell breakdown following chemotherapy.

It is a common complication of hematological tumors which have a high proliferation index, for example, Burkitt's lymphoma, hyper-leukocytic acute myelogenous leukemia (AML), diffuse large B-cell lymphoma.

This releases a large quantity of intracellular components such as potassium, phosphate and uric acid.

## Association:

- Acute leukaemia.
- High-grade NHL.
- **Pre-treatment** ↑ level of **LDH** as it corresponds with tumour bulk.

## Complications: (Like rhabdomyolysis)

- **Hyper**kalemia
- **Hyper**phosphatasemia
- **Hyper**uricemia
- **Hypo**calcemia
- Acute renal failure

## Management:

- Prevention by **good hydration 3 L/m2** before starting chemotherapy (about 4-6 L per day).
- Dietary modification: ↓ K in diet.
- ↑ Uricemia → urine alkalinization and **allopurinol**.
- Osmotic diuresis is **NOT** first line therapy may contribute to precipitation of uric acid in renal tubules.
- **Rasburicase** (a recombinant version of urate oxidase, an enzyme which catalyses the conversion of uric acid to allantoin, this allantoin is 5-10 times more soluble than uric acid, so renal excretion is more effective) is often given before the chemotherapy to reduce the risk of this occurring.

**ATLS Treatment >>> Intravenous hydration** with 3 L/m2 and **Rasburicase**

# Superior vena cava (SVC) obstruction

It is an **oncological emergency** caused by compression of the SVC.

It is most commonly associated **with lung cancer**.

## Features:

- **Dyspnea** is the most common symptom
- Swelling of the face, neck and arms - conjunctival and periorbital oedema may be seen
- Headache
- Visual disturbance
- Pulseless jugular venous distension

## Causes:

- Common malignancies: **small cell lung cancer**, lymphoma.
- Other: metastatic seminoma, Kaposi's sarcoma, breast cancer.
- Aortic aneurysm
- Mediastinal fibrosis
- Goitre
- SVC thrombosis

## Management:

- General: Dexamethasone, balloon venoplasty, stenting
- Small cell: chemotherapy + radiotherapy
- Non-small cell: radiotherapy

Any Pt with malignancy or even disseminated malignancy and unknown primary, presents with oedema of the arms and face, persistent headache, with dilated neck veins >>> you suspect superior vena cava obstruction (SVCO).
Up to 4% of patients with lung cancer will develop SVCO at some point during their disease. Up to 10% of SCLC will present with SVCO.
**Both Non-small** cell cancer and **small** cell malignancy may cause SVCO.
SVCO is much more likely to be associated with **right sided lung lesion 4** times than with left sided lesions.
**SVCO** >>> It is an **oncological emergency**.
CXR is abnormal in around 85% of cases, mediastinal widening is common.
Mediastinal **radiotherapy** leads to **symptomatic relief** in **80% of patients**, although case studies have shown this does not always correlate to patency of the superior vena cava.
Radiotherapy is useful but its effects are **not quick** enough.
If possible, an attempt should be made to obtain a **tissue diagnosis**, as some tumours respond to radiotherapy whereas others are more sensitive to chemotherapy.
Tumours which are very chemosensitive, such as germ cell and lymphoma, can cause SVCO.
**Dexamethasone IV** at **high** dose is of benefit in **severe** cases of SVCO + **LMWH**.
It is important to note that in 2004 NICE recommended considering **stenting** in the majority of cases of SVCO. This is a **minimally invasive** procedure which **relieves** symptoms **quicker than** chemotherapy or radiotherapy.
**SVCO >>> immediate management >>> Dexamethasone IV + LMWH.**

In **70%** of testicular tumours either **Beta-HCG** which is raised in seminomatous germ cell tumours or **AFP** which is raised in non-seminomatous germ cell tumours.
The incidence of testicular tumours is **2-3 cases / 100,000 men per year** and they account for **1-2% of all cancers in males**.
Average age at presentation is **20-44 years old**.

**Testicular Seminoma:**
It is a germ cell tumour (**GCT**), testicular GCTs are **rare**.
They are the most common malignancy in men aged **15-35** years old.
The most common presentation is with a **painless** testicular **lump** that has been present for several days to months.
**Cryptorchidism** is associated with a greatly increased risk of seminoma (10-40 times), although surgery in many cases permits earlier detection of the tumour.
Around 75% of patients present with localised disease, 15% regional LN involvement, and around 10% with distant metastasis (e.g. to lungs).
**Scrotal US** is the investigation of **choice**: typically a **hypoechoic mass** with areas of **calcifications**.
**Beta-HCG** is the most specific tumour marker for Testicular Seminoma, however it is **only** elevated in 5-10% of cases, and the level of elevation correlates with **metastasis**.
Due to commonality between B-HCG and TSH, profound rise in B-HCG result in **hyperthyroidism (↓↓ TSH)** so symptoms of weight loss and anxiety.
Testicular biopsy is not recommended.
**Treatment**: **Orchiectomy**.

**Treatment**: Orchiectomy ± Radiotherapy or chemotherapy.
**Bleomycin** is an antimitotic agent used for the ttt of **testicular tumours** and a serious SE is **pulmonary fibrosis.**

## Spinal cord compression

Spinal cord compression is an oncological emergency and affects up to 5% of cancer patients.
Extradural compression accounts for the majority of cases, usually due to vertebral body metastases. It is more common in patients with lung, **breast** and prostate cancer.

**Features:**

- **Back pain** - the **earliest** and **most common** symptom - may be **worse on lying down and coughing.**
- Lower limb weakness.

- Sensory changes: sensory loss and numbness
- Neurological signs depend on the level of the lesion:
  - Lesions above L1 usually result in UMNL signs in the legs and a sensory level.
  - Lesions below L1 usually cause LMNL signs in the legs and perianal numbness. Tendon reflexes tend to be increased below the level of the lesion and absent at the level of the lesion.

### Management:

- **High-dose oral dexamethasone.**
- Urgent oncological assessment by **urgent MRI** for consideration of radiotherapy or surgery.

Suspected Spinal cord compression >>> Oral dexamethasone + Urgent MRI

Metastatic bone pain >>> may respond to **NSAIDs**, **bisphosphonates** or **radiotherapy**

## Palliative care prescribing: pain

### NICE guidelines:

In 2012 and updated in 2016 NICE published guidelines on the use of opioids in palliative care.

### Starting treatment:

- When starting treatment, offer patients with advanced and progressive disease regular oral modified-release (MR) or oral immediate-release morphine (depending on patient preference), with oral immediate-release morphine for breakthrough pain.
- If no comorbidities use 20-30mg of MR a day with 5mg morphine for breakthrough pain. For example, 15mg modified-release morphine tablets twice a day with 5mg of oral morphine solution as required.
- Oral modified-release morphine should be used in preference to transdermal patches.
- **Laxatives** should be prescribed for all patients initiating strong opioids.
- Patients should be advised that nausea is often transient. If it persists then an antiemetic should be offered.

### SIGN guidelines:

SIGN issued guidance on the control of pain in adults with cancer in 2008.

- The breakthrough dose of morphine is one-sixth the daily dose of morphine.
- All patients who receive opioids should be prescribed a laxative.

- Opioids should be used with caution in patients with chronic kidney disease. **Alfentanil, buprenorphine** and **fentanyl** are the preferred opioids in CKD.
- Metastatic bone pain may respond to NSAIDs, bisphosphonates or radiotherapy.

## Other points:

When increasing the dose of opioids the next dose should be increased by 30-50%.

## Opioid side-effects:

| Usually transient | Usually persistent |
|---|---|
| Nausea<br>Drowsiness | Constipation |

### Conversion between opioids:

| From | To | Conversion factor |
|---|---|---|
| Oral codeine | Oral morphine | Divide by 10 |
| Oral tramadol | Oral morphine | Divide by 10* |

**Oxycodone generally causes less sedation, vomiting and pruritis than morphine but more constipation.**

| From | To | Conversion factor |
|---|---|---|
| Oral morphine | Oral oxycodone | Divide by 1.5-2** |

## The current BNF gives the following conversion factors for transdermal perparations:

- **A transdermal fentanyl 12 microgram patch** equates to approximately **30 mg oral morphine daily.**
- A transdermal buprenorphine 10 microgram patch equates to approximately 24 mg oral morphine daily.

| From | To | Conversion factor |
|---|---|---|
| Oral morphine | Subcutaneous diamorphine | Divide by 3 |
| Oral oxycodone | Subcutaneous diamorphine | Divide by 1.5 |

*This has previously been stated as 5 but the current version of the BNF states a conversion of 10

**Historically a conversion factor of 2 has been used (i.e. oral oxycodone is twice as strong as oral morphine). The current BNF however uses a conversion rate of 1.5

Morphine acts for 4 to 5 hours while pethidine works for 2 to 3 hours.

This means that **pethidine** would have to be given at **more frequent intervals** to produce the same analgesic effects as morphine.

**Morphine** is **effective for the treatment of most types of pain** especially when given in combination with NSAIDs for bone pain or gabapentin for neuropathic pain.

Morphine is extensively metabolised in the liver to morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G).

M6G appears to have analgesic effects and it is 2 to 4 times more potent than morphine. **M6G** is primarily **excreted by the kidneys**, thus accumulation occurs in renal failure and is likely to cause **opioid toxicity**.

**Fentanyl** is a **synthetic opioid** extensively metabolised by cytochrome P450 enzymes in the **liver** and gastrointestinal tract, thus **it is unaffected by renal impairment**. Due to its extensive first pass metabolism, it can only be given parenterally (that is, transmucosal, transdermal, IM, IV or SC).

So **Fentanyl injection is safe in cases of renal impairment.**

**Transdermal** fentanyl alone has **no** place for the treatment of **acute pain**; as steady state will only be obtained more than 24 hours post-application.

## Palliative care prescribing: agitation and confusion

Underlying causes of confusion need to be looked for and treated as appropriate, for example hypercalcaemia, infection, urinary retention and medication. If specific treatments fail then the following may be tried:

- first choice: haloperidol
- other options: chlorpromazine, levomepromazine

In the terminal phase of the illness then agitation or restlessness is best treated with midazolam

## Palliative care prescribing: hiccups

### Management of hiccups

- chlorpromazine is licensed for the treatment of intractable hiccups
- haloperidol, gabapentin are also used
- dexamethasone is also used, particularly if there are hepatic lesions
  - In the presence of hepatic or cerebral cancer a trial of dexamethasone may induce some remission

# Palliative care prescribing: secretions

These are common in the last days of life, but are generally more troubling for family members than for the patient themselves.

## Management

### Conservative:

- Avoiding fluid overload - particularly stopping IV or subcutaneous fluids
- Educating the family that the patient is likely not troubled by secretions

## Medical:

- hyoscine hydrobromide or hyoscine butylbromide is generally used first-line
  - neither the BNF nor NICE Clinical Knowledge Summaries suggest one is first-line over the other
  - hyoscine butylbromide may be less sedative than hyoscine hydrobromide
- glycopyrronium bromide may also be used

# Palliative care prescribing: nausea and vomiting

## Opiate induced nausea

### Haloperidol

- 90% of patients taking morphine require antiemetics (morphine stimulates D2 receptors in the CTZ).
- **Haloperidol is the first-choice antiemetic for opiate induced nausea in the palliative care setting.**
- Haloperidol acts as a central dopamine (D2-receptor) antagonist. The chemoreceptor trigger zone (CTZ) is rich in dopaminergic receptors. Opioid related nausea is thought to be predominantly due to dopamine pathways in the CTZ.
- **haloperidol >> dopamine receptor antagonist (D2) activity >> drug-induced parkinsonism (DIP).**

### Post-chemotherapy or radiotherapy induced nausea

- **Ondansetron** ($5HT_3$ antagonist) is mainly used in post-chemotherapy or radiotherapy induced nausea.
- In UK $5HT_3$ antagonists are licensed only for post-chemotherapy and post-operative nausea.
- **Which antiemetics is most useful following treatment with a platinum-based chemotherapy?** >> **Ondansetron**
  - Examples of platinum-based chemotherapies are cisplatin, carboplatin and oxaliplatin

**Nausea associated with cerebral disease (brain metastases)**

- **If he patient's history raises the possibility of brain metastases, cyclizine would be the most appropriate first line agent.**
  - It targets the dopamine and cholinergic receptors and is widely accepted as the best antiemetic for nausea associated with cerebral disease.

**Treatment of vomiting associated with breast cancer chemotherapy**

- modern palliative chemotherapy for breast cancer would be **unlikely to cause severe nausea and vomiting.**
- The patient may have **anticipatory vomiting** (before attending for treatment) almost certainly associated with anxiety about chemotherapy. Therefore, treatment with a **benzodiazepine as an anxiolytic as well as an antiemetic** would be the most logical.

## Palliative care prescribing: Constipation

### Causes

- Constipation is common in patients with advanced cancer, particularly in those taking opioid medication, with reduced oral intake and reduced mobility.
- Hypercalcaemia can cause constipation (**a constipation in cancer → do blood tests, including bone profile**)
  - Hypercalcaemia is a common problem in palliative care.
  - prostate cancer with bone metastasis is a frequent cause.

### Treatment

**Polyethylene glycol (Movicol) would seem the best choice in this scenario.**

- It has an osmotic action and helps to retain water in the gut to aid faecal passage.
- It is generally better tolerated than some other oral laxatives and has been shown to be more effective than lactulose in the management of chronic constipation.

**Lactulose (an osmotic laxative)** is usually avoided in palliative care

- as it can cause abdominal cramps and excessive flatulence.
- Its sweet taste can be unpalatable for some patients
- it needs to be consumed with large volumes of liquid which is sometimes not practical for palliative care patients.

**Co-danthramer** is a combination of danthron (a stimulant laxative) and poloxamer (a stool softener) and is a popular choice for constipation in

palliative care. It is **licensed only for use in patients with a terminal illness** and should not be given to those who are incontinent (of urine or faeces) due to the risk of developing a 'danthron burn' through prolonged contact with the skin.

## Opioid toxicity in palliative care

**Most opiates are renally excreted, leading to opiate toxicity. Fentanyl, buprenorphine and methadone are metabolised by the liver and are therefore safer in renal failure**

**Transdermal fentanyl absorption is increased by heat (e.g. hot water bottle) or pyrexia, potentially leading to opioid toxicity**

### May be precipitated by:

- **Renal impairment with renally excreted opiates**
- **increase transdermal fentanyl absorption by heat eg: fever**
- reduction in opioid requirement. This is a common occurrence in patients who **have radiotherapy for bone metastases** if their medication dose is not adjusted.

### Features:

- **Reduced conscious level, hallucinations, vomiting, myoclonic jerks and pinpoint pupils.**

### Management

- **stop the long acting opioid temporarily to allow the excess drug to be excreted and then rely on short acting opioid for any breakthrough pain that might occur.**
  - once the patient recovered, the long acting opioid can be reintroduced at a much-reduced dose.
- Although the patient is opioid toxic, giving naloxone would not usually be the right thing to do.
  - Naloxone antagonises opioid receptors in the nervous system and this can cause patients significant pain and distress as their analgesia is reversed.
  - Unless the patient is in a peri-arrest situation where use of naloxone could be justified, it is better simply to withdraw the regular opioid until the patient recovers.

## Palliative care: Breathlessness

**Opioids are the first line treatment to reduce the sensation of breathlessness in Palliative care**

- Breathlessness is a significant problem in the palliative care setting and not just in patients with lung cancer.
- Palliation of breathlessness involves:

**First-line: Opioids**

- **Opioids are very effective agents to reduce the sensation of breathlessness** - they reduce inappropriate respiratory drive.
- They rarely cause respiratory depression when used correctly.

**Second line: Benzodiazepines** (effective agents after opioids).

**Other therapies:**

- **Psychological support and physiotherapy**
  - are very useful adjuncts to medications.
  - However, these **take time** and if the patient is distressed, they are not helpful in the immediate cases (unless breathing techniques have been taught).
- **Oxygen**
  - has a small role in the management of breathlessness in palliative medicine, unless the patient is hypoxic.
  - It can be necessary when patients become psychologically dependent on supplementary
  - oxygen.

## Palliative care: end of life care

**Glucocorticoids are prominent in end of life care**

**Benefits of steroids**

- Improve general feelings of wellbeing
- Relive fatigue and improve energy
- Relive nausea
- Control of pain
  - 15% improvement in pain
  - **If the patient is unable to obtain satisfactory pain relief despite an escalating opiate regimen >> Commence trial with dexamethasone**

- One of the sources of pain associated with liver metastases is due to **stretching and irritation of the liver capsule for which a trial of dexamethasone may provide an analgesic effect.**
- Liver capsule pain tends not to be opioid responsive, therefore increasing the modified or immediate release morphine would not be the correct option.

**Dexamethasone is the usual agent of choice**

**The most important aspect of management is to try to keep the patient calm and relieve distress with a large dose of midazolam (10mg).**

- **In a massive terminal haemorrhage**, a large dose of **midazolam** (10mg) can be given as part of 'crisis management' to relieve distress. Red or green towels or blankets should be available to soak up and mask the colour of blood

## Positron Emission Tomography (PET)

Positron Emission Tomography (PET) is a form of nuclear imaging which uses fluorodeoxyglucose (FDG) as the radiotracer.
This allows a 3D image of metabolic activity to be generated using glucose uptake as a proxy marker.
The images obtained are then combined with a conventional imaging technique such as CT to decide whether lesions are metabolically active.

### Uses

evaluating primary and possible metastatic disease
cardiac PET: not used mainstream currently

## Leukocyte alkaline phosphatase (LAP) score

The LAP score aids in the differential diagnosis of CML versus leukemoid reaction.

**It also aids in the evaluation of:**

- Polycythaemia vera
- Myelofibrosis with myeloid metaplasia, and
- Paroxysmal nocturnal haemoglobinuria.

**High scores have been seen in:**

- **Leukaemoid reactions.**
- **Polycythaemia vera.**
- **Myelofibrosis.**

- Aplastic anemia.
- Downs syndrome
- Hairy cell leukemia.
- Neutrophilia either physiological or secondary to infection.
- Hodgkin disease.

**Low** scores have been associated with:

- CML
- Paroxysmal nocturnal haemoglobinuria (PNH)
- Thrombocytopenic purpura (TTP), and
- Hereditary hypophosphatasia.

**Leucocyte alkaline phosphatases(summary)**

| Raised in | Low in |
|---|---|
| • **Infections.**<br>• **Leukemoid reaction.**<br>• **Polycythemia rubra vera.**<br>• **Myelofibrosis.**<br>• **Steroids, Cushing's syndrome**<br>• **Pregnancy, OCP** | • **CML**<br>• **PNH**<br>• **TTP**<br>• **Pernicious anemia** |

## ECOG score

The ECOG score is a 'performance status' scale, or a score that measures the functional status a patient.
It is **used to decide if a patient is a good or poor candidate for future oncological therapies.**
Those with a poor functional status is a poor candidate for further chemotherapy.

| | |
|---|---|
| 0 | Fully active, able to carry on all pre-disease performance without restriction |
| 1 | Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work |
| 2 | Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours |
| 3 | Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours |
| 4 | Completely disabled; cannot carry on any selfcare; totally confined to bed or chair |
| 5 | Dead |

# POEMS syndrome

It is **P**olyneuropathy, **O**rganomegaly, **E**ndocrinopathy, **M**onoclonal gammopathy and **S**kin changes.

It is a **rare multisystem** disease that occurs in the setting of **plasma cell dyscrasia.**

The pathophysiology of this disease is not **known**; however, elevated levels of cytokines and growth factors have been implicated.

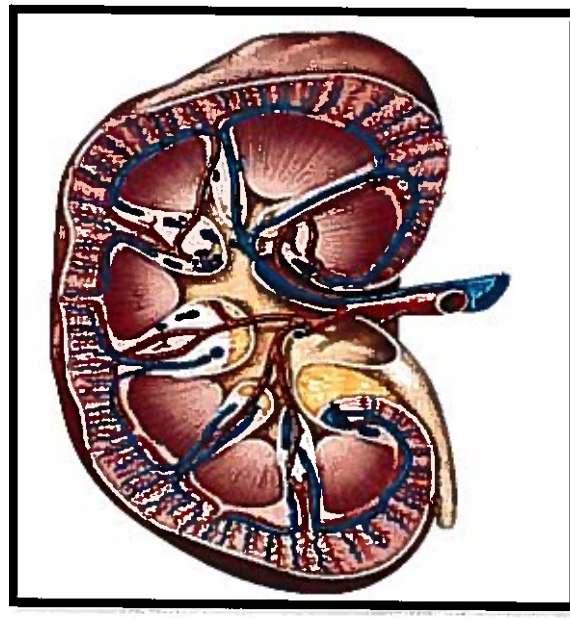
**Polyneuropathy**: bilateral symmetric disturbance, it involves both motor and sensory nerves, begins distally and has a progressive proximal spread. Both demyelination and axonal degeneration are noted. Cranial or autonomic nerves are not involved.

**Organomegaly: Liver, spleen & LN.**

**Multiple Endocrinopathy** e.g. **thyroid.**

**Gammopathy**: e.g. **MGUS**, but classical Myeloma is not usually associated.

# Nephrology



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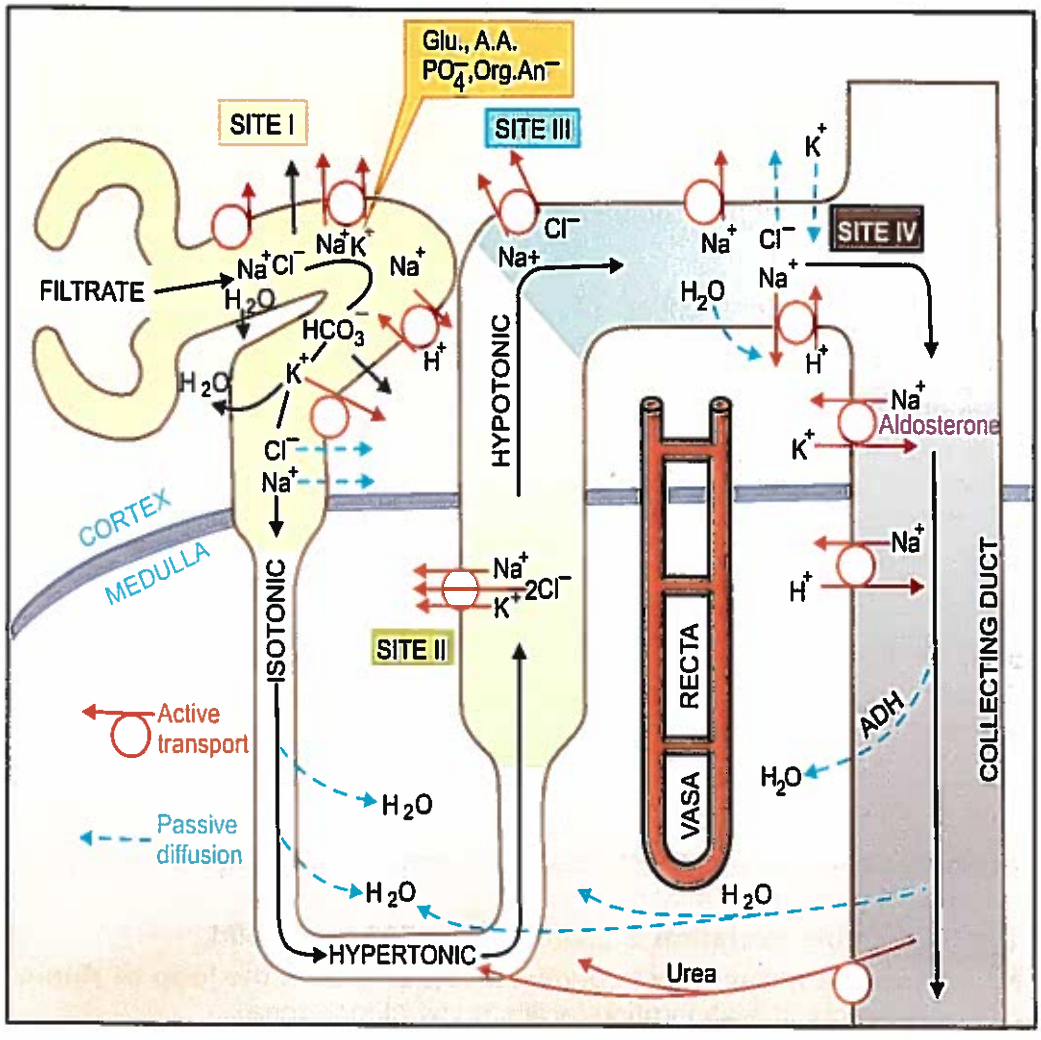
# Anatomy and physiology




Diagrammatic representation of nephron showing the four sites of solute reabsorption.
The thick ascending limb of loop of Henle is impermeable to water; Glu—Glucose; A.A.—Amino acid; Org. An.—Organic anions.

- Renal blood flow (**RBF**) is approximately **25%** of cardiac output.
- The **'Fick principle'** can be used to estimate RBF through **clearance**.
- RBF is higher in the **cortex** than medulla as one might expect with the increasing **glomeruli** in this region.
- **Sympathetic** stimuli produce **vasoconstriction** and RBF should be **increased** in response to **hypoxia**.

**Renal imaging:**

**Renal scintigraphy** with **DMSA scan** **(dimercaptosuccinic acid DMSA)** involves administration of radioactive isotope which is avidly taken up by the renal parenchyma.

This permits the identification of regions of **decreased uptake** that may represent **acute inflammation** (such as **pyelonephritis**) or **renal scarring,** also allows detection of **congenital renal disorder.**
A **small kidney** with **uniform** uptake of DMSA is likely to represent **congenital hypodysplasia,**
Whereas a **focal area** of **reduced** cortical uptake associated with loss of contours is more likely to represent an **infection-related scar.**
So the **best** imaging to identify **renal scarring,** for instance after childhood febrile urinary tract infection >>> Renal **DMSA** scintigraphy.

**Renal DTPA** involves an isotope that is **exclusively filtered by the glomeruli**, and is used to give a **"perfusion index"** and **evaluate excretion** (**obstruction** assessment) of the kidney.

**Voiding cystourethrography (VCUG)** is used to determine whether there is vesicoureteral reflux (**VUR**).

- **Arginine vasopressin (AVP)** acts on the **collecting ducts** increasing permeability to water.
- The **total solute excretion** is approximately **700 mosmol/d.**
- **Na reabsorption** is **mostly** through **active** transport in **the loop of Henle** with only a modest reabsorption facilitated by aldosterone.
- A **10 minutes period** of **hyperventilation** would cause a **respiratory alkalosis** leading to an **increased secretion of bicarbonate** and **retention of hydrogen ions.**
- The **rate** of **ammonium excretion** is **proportional** to the rate of **hydrogen ion excretion.**

# Renin-angiotensin-aldosterone system (RAAS)

## Adrenal cortex (mnemonic GFR - ACD):

- Zona glomerulosa (on outside): mineralocorticoids, mainly aldosterone.
- Zona fasciculata (middle): glucocorticoids, mainly cortisol.
- Zona reticularis (on inside): androgens, mainly dehydroepiandrosterone (DHEA).

Adrenal cortex mnemonic>>> **GFR - ACD**

The **adrenal medulla** secretes virtually all the **adrenaline** in the body as well as secreting **small amounts of noradrenaline**. It essentially represents an enlarged and specialized sympathetic ganglion

## Renin:

- An enzyme that is **released by the renal juxtaglomerular cells in response to reduced renal perfusion.**
- **Factors stimulating** renin secretion:
  - **Hypotension** causing reduced renal perfusion
  - **Hyponatremia**
  - **Sympathetic nerve stimulation**
  - **Catecholamines**
  - **Erect** posture
- Factors reducing renin secretion:
  - Drugs: **beta-blockers, NSAIDs**
- Renin **hydrolyses angiotensinogen** to **form angiotensin I.**

## Angiotensin II:

- Angiotensin-converting enzyme (ACE) in the lungs converts angiotensin I → angiotensin II.
- Angiotensin II has a wide variety of actions:
  - Causes **vasoconstriction of vascular smooth muscle** leading to raised blood pressure and **vasoconstriction of efferent arteriole of the glomerulus** → increased filtration fraction (FF) to preserve GFR. Remember that FF = GFR / renal plasma flow.
  - **Stimulates thirst** (via the hypothalamus).
  - **Stimulates aldosterone and ADH** release.
  - **Increases proximal tubule $Na^+/H^+$** activity.

### Aldosterone:

- Released by the **zona glomerulosa** in response to raised **angiotensin II, potassium, and ACTH levels.**
- **Causes retention of $Na^+$** in exchange for $K^+/H^+$ in distal tubule.

### Contraindications to ACE inhibition include:

- **Pregnancy** or **wants to start a family**
- **Breast feeding**
- **Significant renal artery stenosis.**
- **Angio-oedema**

## Renal Biopsy

- For a routine biopsy there is **no preferable side to biopsy**, but commonly it is the Lt Kidney.
- **Coagulation studies** should always be performed prior to renal biopsy due to the risk of bleeding (e.g. in a case of alcohol excess, clotting studies may be deranged).
- **Macroscopic haematuria** can occur in up to **10%** of renal biopsies.
- **Nephrectomy** is a rare but serious complication of renal biopsy required to control bleeding. It should be consented for that.

**NB:** The hila of the kidneys lie at the L1 and L2 vertebral levels.

# Acute kidney injury

## Acute kidney injury

### Acute kidney injury is defined as:

- sudden decrease in kidney function occurring over a period of hours to days.
- Manifested by accumulation of waste products including, but not limited to, urea and creatinine in the blood and sometimes accompanied by oliguria.
- The term acute kidney injury is now the preferred term, as it reflects the importance of smaller decrements in kidney function that do not result in complete loss of kidney function.
- the term acute renal failure now describes AKI resulting in sever organ failure with the need for acute renal replacement therapy.
- AKI is present in 5-10% of all hospitalized patients, and up to 30-65% of patients in ICU and 5% of them require dialysis.
- The incidence is increasing at an alarming rate.
- Mortality rate > 50% in dialyzed ICU patients.
- 25% of ICU dialysis survivors progress to ESRD within 3 years.

### The guideline discusses what increases the risk of AKI:

- Emergency surgery, i.e, risk of sepsis or hypovolemia
- Intraperitoneal surgery
- CKD, i.e., if eGFR < 60
- Diabetes
- Heart failure
- Age >65 years
- Liver disease
- Use of nephrotoxic drugs
  - NSAIDs
  - aminoglycosides
  - ACE inhibitors/angiotensin II receptor antagonists
  - Diuretics

### Diagnostic criteria

It also defines the criteria for diagnosing AKI

- Rise in creatinine of 26µmol/L or more in 48 hours OR
- >= 50% rise in creatinine over 7 days OR
- Fall in urine output to less than 0.5ml/kg/hour for more than 6 hours in adults (8 hours in children) OR

- >= 25% fall in eGFR in children / young adults in 7 days.

## Staging criteria

**The Kidney Disease: Improving Global Outcomes (KDIGO) criteria are widely used to stage the AKI:**

| | |
|---|---|
| Stage 1 | Increase in creatinine to **1.5-1.9** times baseline, or<br>Increase in creatinine by ≥26.5 µmol/L, or<br>Reduction in urine output to **<0.5** mL/kg/hour for **≥ 6 hours** |
| Stage 2 | Increase in creatinine to **2.0 to 2.9** times baseline, or<br>Reduction in urine output to **<0.5** mL/kg/hour for **≥12 hours** |
| Stage 3 | Increase in creatinine to **≥ 3.0** times baseline, or<br>Increase in creatinine to ≥353.6 µmol/L or<br>Reduction in urine output to **<0.3** mL/kg/hour for **≥24 hours**, or<br>The initiation of kidney replacement therapy, or,<br>In patients <18 years, decrease in eGFR to <35 mL/min/1.73 m2 |

## Acuter kidney injury network (AKIN) Stages of AKI

| AKIN Stage | Serum Creatinine Criteria | Urine output |
|---|---|---|
| **Risk** | ↑S. Creat ≥ 26.4 Mmol/L or 50-100% above base line | < 0.5 ml/kg/$m^2$ for > 6 hours |
| **Injury** | Increase of 2-3 folds over base line | < 0.5 ml/kg/$m^2$ for > 12 hours |
| **Failure** | Increase of > 3 folds over base line or S. Creatinine > 354 Mmol/L acute or increase of at least 0.5 mg/dl (44 Mmol/L) To a level of serum creatinine more than 4mg/dl or<br>Need RRT | < 0.5 ml/kg/$m^2$ for > 24 hours |

**The stage of loss is defined as**: need for RRT duo to AKI for more than 4 weeks.

**End stage is defined as**: need for RRT duo to AKI for more than 3 months.

## Referral criteria

Refer to a nephrologist if any of the following apply:

- Renal tranplant
- ITU patient with unknown cause of AKI
- Vasculitis/ glomerulonephritis/ tubulointerstitial nephritis/ myeloma
- AKI with no known cause
- Inadequate response to treatment
- Complications of AKI

- Stage 3 AKI (see guideline for details)
- CKD stage 4 or 5
- Qualify for renal replacement hyperkalemia / metabolic acidosis/ complications of uremia/ fluid overload (pulmonary oedema

**Causes of ARF can be divided into pre-renal, renal and post-renal.**

**Pre-renal:**

- Hypovolaemia (gastroenteritis, burns, sepsis, Haemorrhage, nephrotic syndrome congestive heart failure, advanced liver disease.
- The hepatorenal syndrome is a severe form of prerenal azotaemia in patients with cirrhosis of the liver and sever portal hypertension.

**Renal:**

- **Glomerular**: GN
- **Tubular**: ATN, ischaemic, toxic, obstructive
- **Interstitial**: interstitial nephritis, pyelonephritis
- **Vascular**: renal vein thrombosis, RAS, embolus, HUS, vasculitis.

## Rhabdomyolysis

Rhabdomyolysis is a condition characterized by muscle injury leading to myocyte necrosis and the release of intracellular contents into the circulation. The term is usually applied when acute kidney injury results from muscle injury.

Rhabdomyolysis will typically feature in the exam as a patient who has had a fall or prolonged epileptic seizure and is found to have acute renal failure on admission.

**Features:**

- Acute renal failure with disproportionately raised Creatinine
- **Hypocalcemia** (myoglobin binds calcium, serum calcium is bound to damaged muscle, around 20% of patients become hypercalcemia during recovery as this bound calcium is remobilized.) only corrected if symptomatic and /or ionized calcium less than 0.8 mg/dl.
- ↑ **CPK more than 10 times the upper normal level or more than 10000u/l**
- ↑ **Phosphate** (released from myocytes)
- ↑ **K** (because K is released from necrotic myocytes and this is exacerbated in the context of renal impairment and metabolic acidosis).
- **Myoglobinuria.**

**N.B:** CK levels are the most sensitive marker of rhabdomyolysis level tend to rise in the first 12 hours and peak in 1 to 3 days, it remains elevated for 5 days, the risk of AKI is usually low if the level below 10000 u/l, patients who develop AKI at lower levels usually have associated factors such as, sepsis ,hypotension or underlying kidney disease.

## Causes:

- **Seizure**
- **Collapse**/coma (e.g., **elderly patients collapses at home, found 10 hours later or homeless street person)**
- **Ecstasy**
- Crush injury
- McArdle's syndrome
- Drugs: statins (especially if given with drugs that usually increase there level as macrolides and antifungals)

## Management:

- **IV fluids** to maintain good urine output.
- urinary alkalinization is sometimes used.

**NB: Severe hypokalemia** is considered as one of the **causes** of **rhabdomyolysis**. Also, **severe hypophosphatemia** is considered as one of the **causes** of rhabdomyolysis.

## SUMMARY

**potential Mechanisms of Rhabdomyolysis-Inducet Acute Kidney Injury**

| **Vasoconstriction within the Kidney and ischemic Tubular injury** | **Cast Formation** | **Myoglobin Induced Direct Tubular Toxicity** |
|---|---|---|
| Muscle necrosis leads to third spacing, release of endotoxins and cytokines, and volume depletion. | Results from the interaction of Tamm-Horsfall proteins with myoglobin. Formation of casts is enhanced by renal vasoconstriction and low tubular pH. | Heme component of myoglobin is implicated in ischemic tubular injury, ATP depletion. Ox-idative stress, and lipid peroxidation. |
| Hypovolemia results in the activation of RAAS. leading, to renal vasoconstriction. | Cast formation leads to tubular obstruction, thus increasing intraluminal pressure and decreasing glomerular filtration. | Myoglobin-induced tubular toxicity is exac-erbated by hypovolemia and aciduria |
| Hastens cast formation and worsens myoglobin-induced tubular toxicity | | |

**The Authors' Recommendations on the Management of Rhabdomyolysis**

**Suggested Guidelines for the Management of Rhabdomyolysis**

1. Assess likelihood of developing AKI based on the aetiology of rhabdomyolysis and laboratory abnormalities on admission.
2. If the patient is at high risk for AKI, administer IV fluids to target a urine output of >200 mL/hr.
3. NS or LR is the fluid of choice. Bicarbonate should be reserved for patients with acedemia.
4. If bicarbonate is used, target a urine pH >6.5 and closely monitor for hypocalcaemia.
5. Diuretics maybe used for augmentation if the urine output is lower than the desired range despite adequate volume resuscitation.
6. There is no clear current role for prophylactic dialysis for the prevention of rhabdomyolysis-associated AKI, but in the event that KRT is needed, high-flux dialyzers are more efficient at reducing myoglobin levels.

AKI, acute kidney injury, IV, intravenous; LR, lactated Ringer: KRT, kidney replacement therapy, NS, normal saline.

- **tumor lysis syndrome:** Acute on top of chronic renal failure
- **Post-renal:** Obstruction, either congenital or acquired.

## Prerenal uremia vs. Acute Tubular Necrosis (ATN)

**Prerenal azotemia:** is a functional form of AKI that results from diminished kidney perfusion, As there is no parenchymal injury, the hallmark of prerenal azotemia is the rapid normalization of kidney function when renal perfusion is restored, and the patient is oliguric and if not treated with diuretics it is manifest with increase sodium reabsorption.

Prerenal uremia >>>> kidneys hold on to sodium to preserve volume.

| | Pre-renal uremia | Acute tubular necrosis (ATN) |
|---|---|---|
| Urine sodium | < 20 mmol/L | > 40 mmol/L |
| Fractional sodium excretion* | < 1% | > 1% |
| Fractional urea excretion** | < 35% | >35% |
| Urine osmolality | **>500** | **<350** |
| Urine: plasma osmolality | > 1.5 | < 1.1 |
| Urine: plasma urea | > 10:1 | < 8:1 |
| Specific gravity | > 1020 | < 1010 |
| Urine | 'bland' sediment | brown granular casts (NOT RBCS cast |
| Response to fluid challenge | Yes | No |

Fractional sodium excretion = (urine sodium/plasma sodium) / (urine creatinine/plasma creatinine) x 100.
**Fractional urea excretion = (urine urea /blood urea) / (urine creatinine/plasma creatinine) x 100.

Normal plasma osmolality = 278 – 305 mOsmol/Kg
Normal urinary osmolality = 350 – 1000 mOsmol/Kg

Of the acute renal failure seen by physicians 80-90% will fall into the category of pre-renal failure or ATN.
The urinary abnormalities in **ATN** suggest **tubular dysfunction** (that is, urinary sodium greater than 40 mmol/L, low urinary osmolality less than 350 mOsmol/L).

Oliguria is defined as <400 ml urine/day.

## Cholesterol embolization

### Overview:

- Cholesterol embolization is a well-documented **complication of coronary angiography.**
- Precipitating factors includes: angiography, CABG, anticoagulation and thrombolysis.
- Cholesterol emboli may break off causing **renal** disease.
- Seen more commonly in arteriopathy, abdominal aortic aneurysms.

### Features:

- Renal failure
- Eosinophilia
- Purpura
- Livedo reticularis
- Low C3.
- ↑ESR.
- Urine proteinuria.

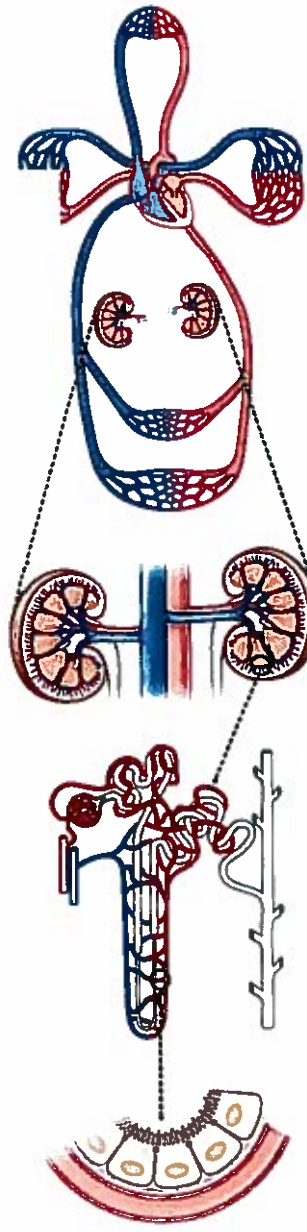
## causes of Postoperative AKI

**Hemodynamic perturbations**
- Effect of CPB circuit
- Low cardiac output
- Blood pressure
- Venous pressure
- Preload/volume
- Anemia/hemolysis
- Ischemia/reperfusion

**Mechanical factors**
- Emboli
- Arterial obstruction
- Venous congestion
- Perfusion pressure
- Abdominal hypertension

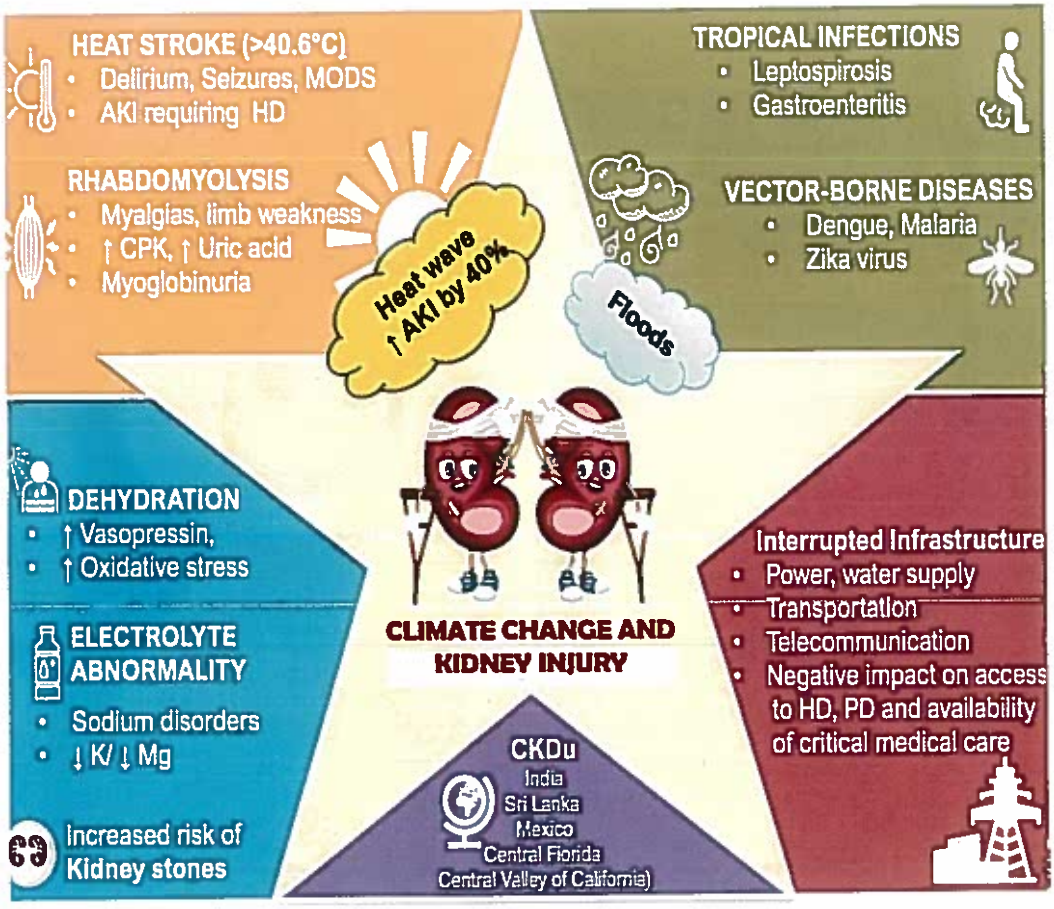
**Other mechanisms**
- Neurohormonal
- Vasoconstriction
- Venous congestion
- Tubular toxicity

**Inflammation/Immunity**
- Inflammation
- Oxidant stress
- Complement activation
- Toxins/drugs
- Contrast media



Major pathophysiologic processes contributing to AKI after vascular and cardiac surgery.

## Climate changes and AKI

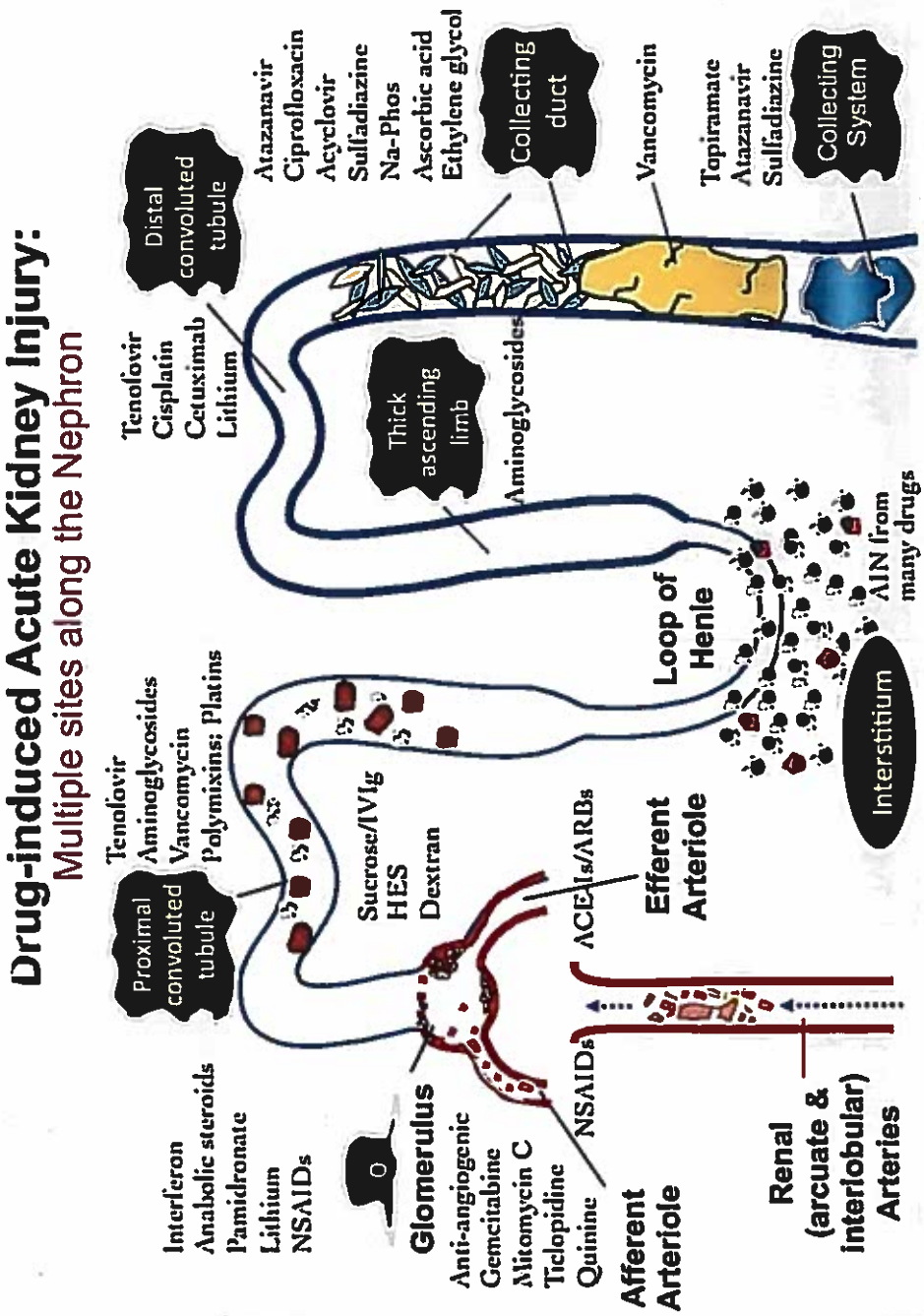


## CARDIORENAL SYNDROMES


Primary disease
Secondary disease
Type 1: Acute CRS
Type 2: Chronic CRS
Type 3: Acute RCS
Type 4: Chronic RCS
Type 5: Secondary CRS
Alteration of renal perfusion is the main trigger (in particular when congestive heart failure is present)
Renal fibrosis is particularly important in type 2. Also to be considered drug induced renal toxicity and VAD induced renal effects
Salt and water, neuro-hormonal and uremia induced dysregulations are the most important aspects
Hypertension, CKD induced myopathy, chronic hemodialysis and fluids shifts may be in cause
Common pathogenetic patterns (i.e. auto-immunity, micro-circulatory dysfunction, cytokine release)

Schematic representation of the five Cardiorenal syndrome (CRS) types according to the organ direction (primary > secondary disease) and the time window (acute or chronic). According to this classification, two CRS (acute and chronic), two renocardiac (acute and chronic) syndromes, and one secondary CRS are depicted.
CKD, chronic kidney disease; RCS, renocardiac syndrome; VAD, ventricular assist device.

## DRUG INDUCED AKI



## Abdominal compartment syndrome:

This syndrome is caused by an increase in intra-abdominal pressure, resulting in the dysfunction of multiple organs including decreased cardiac output and hypotension, and impaired ventilation and decreased visceral perfusion, which in turn may lead to intestinal ischemia ,and infarction and oliguric AKI, mostly due to increased renal venous pressure.
it is thought to cause more than 30% of cases of AKI in critically ill patients.
Diagnosed by increased intraabdominal pressure more than 20mm/Hg, and single organ failure that was not previously present.

**Causes:** trauma with intraabdominal haemorrhage, abdominal surgery, retroperitoneal haemorrhage
peritonitis, pancreatitis, massive fluid resuscitation, abdominal banding repair of large incisional hernia. **Treatment is** abdominal decompression by paracentesis or surgical decompression.

# Contrast Nephrotoxicity

Contrast nephrotoxicity is defined as a **25%** increase in **serum creatinine** occurring **within 3 days** of the intravascular administration of contrast media.

Studies have shown that **contrast induced nephropathy** is most likely to occur **48 to 72 hours after** the administration of IV contrast.

According to the latest guidelines, the need for a **gadolinium**-based contrast study should be **carefully** considered in any patient with CKD stage 3 or greater.

There is a high risk for this condition of **nephrogenic systemic fibrosis (NSF)** with potentially **fatal** consequence. Because of a higher dose requirement of gadolinium in angiography, the odds of NSF are even higher for the patient.

This toxicity of gadolinium **cannot be** circumvented by hydration or N-Acetylcysteine; they are considered to be more appropriate for preventing radio contrast-induced nephropathy.

So patient with CKD >>> the **magnetic resonance angiography (MRA)** with **gadolinium** is **not recommended** because it carries **a risk of nephrogenic systemic fibrosis (NSF), dialysis for 3-5 successive sessions can remove up to 99% of the gadolinium but the risk is still there.**

About **5%** of patients undergoing **cardiac catheterization** experience **contrast-induced renal dysfunction.**

**Metformin** should be stopped **24 hrs. prior** to coronary angiography and reinstated **48 hrs. after** the procedure if renal functions are found to be normal.

**ACEIs AND DIURETICS** are associated with increased risk of contrast nephropathy, most cardiologists therefore discontinue these prior to the procedure.

## Risk factors include:

- Known renal impairment (especially diabetic nephropathy)
- Age > 70 years
- Dehydration
- Cardiac failure
- The use of nephrotoxic drugs such as NSAIDs.

## Prevention:

- Ensure adequate **hydration.**
- **Stop nephrotoxic medications** at least 48 hours prior to the planned procedure (such as NSAIDs and Lasix).
- **N-Acetylcysteine** (usually given **orally**) has been shown to reduce the incidence of contrast-nephropathy (**600 mg x 2 x 2**).
- IF NOT AVILABLE use VIT.C 2 GRAMS BEFORE AND 3 GRAMS AFTER THE PROCEDURE.
- $MgSo_4$ 2 grams over 6 hours before the procedure found to be effective in reducing the tubular injury duo its membrane stabilization characteristics but the evidence needs further studies.

There is no evidence that NaHCO3 reduce the chance of nephrotoxicity.
There is nothing to suggest that changing from oral to an insulin sliding scale to improve glycaemic control can reduce the risk.

## Dialysis and CIN:

**Current evidence showed that there is no what is called prophylactic dialysis.**

- Some evidence of effectiveness of dialysis in stage 3 CKD performed before and after the procedure.
- Few studies from Japan adopted CRRT DURING the procedure to remove the contrast in timely fashion but cannot be used as guidelines, ALTHOUGH THE RESULTS ARE VERY PROMISING WITH ZERO INCIDENCE FOR CIN.

# Acute interstitial nephritis

Acute interstitial nephritis accounts for 25% of drug-induced acute kidney injury.

## Causes

- drugs: the most common cause, particularly antibiotics
  - penicillin
  - rifampicin
  - NSAIDs
  - allopurinol
  - furosemide
  - Proton pump inhibitors.
- systemic disease: SLE, sarcoidosis, and Sjögren's syndrome
- infection: Hanta virus , staphylococci

## Pathophysiology

- histology: marked interstitial oedema and interstitial infiltrate in the connective tissue between renal tubules

## Features

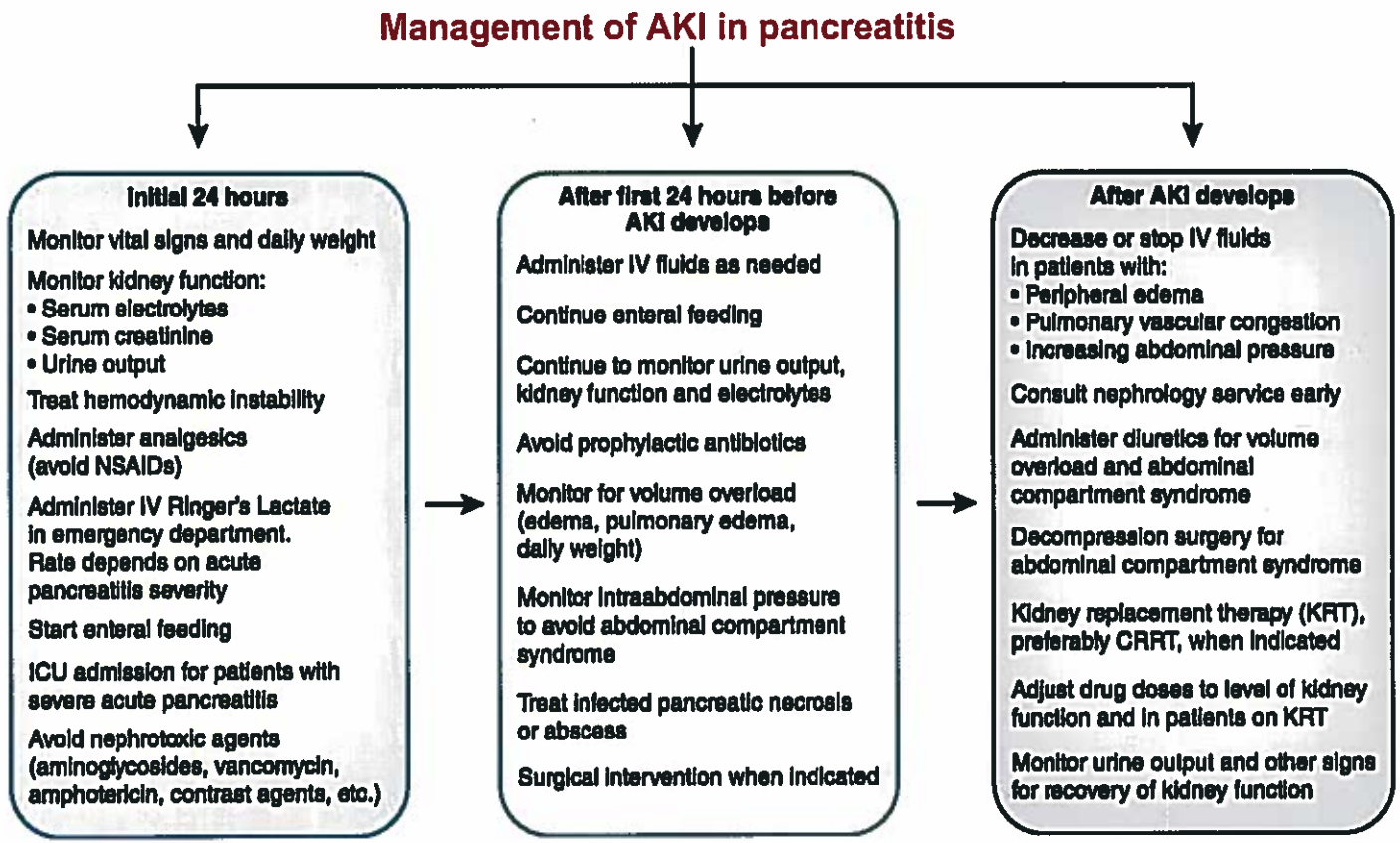
- fever, rash, arthralgia
- eosinophilia
- mild renal impairment
- hypertension

## Investigations

- sterile pyuria
- white cell casts

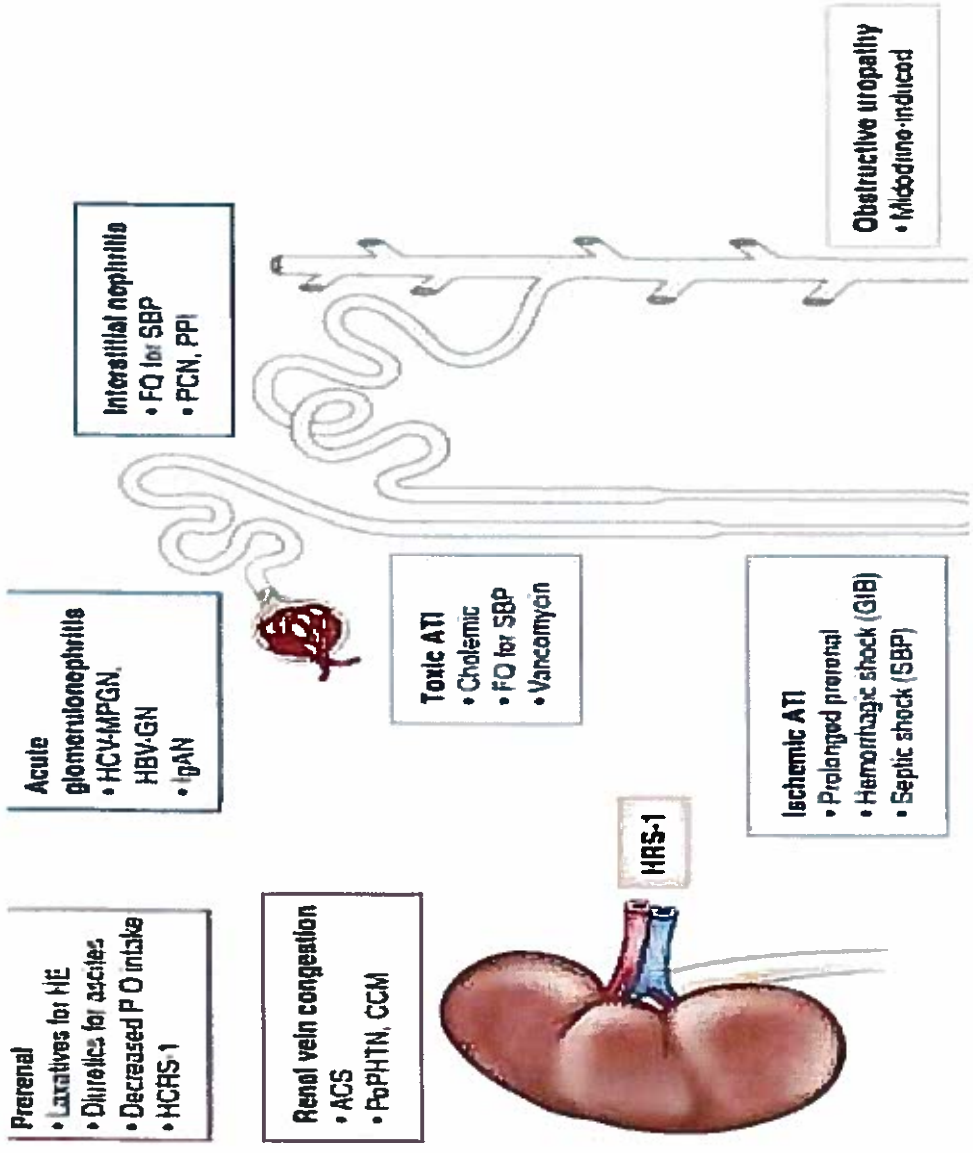
## Tubulointerstitial nephritis with uveitis

Tubulointerstitial nephritis with uveitis (TINU) usually occurs in young females. Symptoms include fever, weight loss and painful, red eyes. Urinalysis is positive for leukocytes and protein.


Management of AKI in pancreatitis
Initial 24 hours
Monitor vital signs and daily weight
Monitor kidney function:
• Serum electrolytes
• Serum creatinine
• Urine output
Treat hemodynamic instability
Administer analgesics (avoid NSAIDs)
Administer IV Ringer's Lactate in emergency department. Rate depends on acute pancreatitis severity
Start enteral feeding
ICU admission for patients with severe acute pancreatitis
Avoid nephrotoxic agents (aminoglycosides, vancomycin, amphotericin, contrast agents, etc.)
After first 24 hours before AKI develops
Administer IV fluids as needed
Continue enteral feeding
Continue to monitor urine output, kidney function and electrolytes
Avoid prophylactic antibiotics
Monitor for volume overload (edema, pulmonary edema, daily weight)
Monitor intraabdominal pressure to avoid abdominal compartment syndrome
Treat infected pancreatic necrosis or abscess
Surgical intervention when indicated
After AKI develops
Decrease or stop IV fluids in patients with:
• Peripheral edema
• Pulmonary vascular congestion
• Increasing abdominal pressure
Consult nephrology service early
Administer diuretics for volume overload and abdominal compartment syndrome
Decompression surgery for abdominal compartment syndrome
Kidney replacement therapy (KRT), preferably CRRT, when indicated
Adjust drug doses to level of kidney function and in patients on KRT
Monitor urine output and other signs for recovery of kidney function

Management of AKI in acute pancreatitis requires a multidisciplinary approach that begins in the emergency department. This involves providing supportive care, close monitoring of kidney function and treatment of pancreatitis related complications. Escalation of therapy to a higher level of care, providing KRT and surgical treatment might be required if the initial therapy fails. CRRT, continuous RRT; ICU, intensive care unit; IV, intravenous; NSAIDs, nonsteroidal anti-inflammatory drugs

## SUMMARY OF CAUSES OF AKI

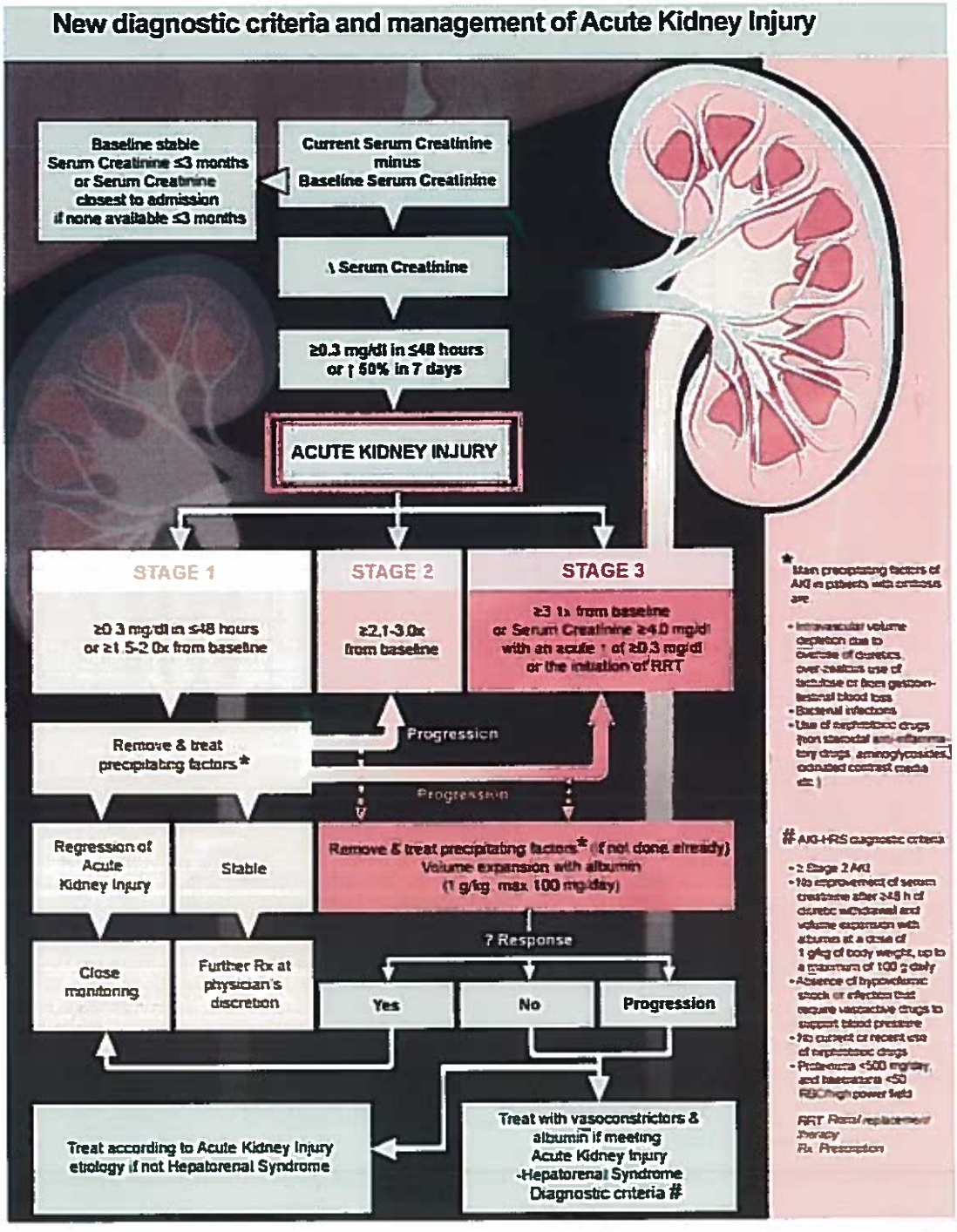



## Preventing AKI

By identifying patients at increased risk of AKI (see above) it may be possible to take steps to reduce the risk. For example, patients who are at risk of AKI and who are undergoing an investigation requiring contrast are usually given IV fluids to reduce the risk.

Certain drugs such as ACE inhibitors and ARBs may also be temporarily stopped.

## Summary of AKI criteria and management


New diagnostic criteria and management of Acute Kidney Injury
Baseline stable
Serum Creatinine ≤3 months
or Serum Creatinine
closest to admission
if none available ≤3 months
Current Serum Creatinine
minus
Baseline Serum Creatinine
↑ Serum Creatinine
≥0.3 mg/dl in ≤48 hours
or ↑ 50% in 7 days
ACUTE KIDNEY INJURY
STAGE 1
≥0.3 mg/dl in ≤48 hours
or ≥1.5-2.0x from baseline
STAGE 2
≥2.1-3.0x
from baseline
STAGE 3
≥3.1x from baseline
or Serum Creatinine ≥4.0 mg/dl
with an acute ↑ of ≥0.3 mg/dl
or the initiation of RRT
Remove & treat
precipitating factors*
Progression
Progression
Regression of
Acute
Kidney Injury
Stable
Remove & treat precipitating factors* (if not done already)
Volume expansion with albumin
(1 g/kg max 100 mg/day)
? Response
Close
monitoring
Further Rx at
physician's
discretion
Yes
No
Progression
Treat according to Acute Kidney Injury
etiology if not Hepatorenal Syndrome
Treat with vasoconstrictors &
albumin if meeting
Acute Kidney Injury
-Hepatorenal Syndrome
Diagnostic criteria #
* Main precipitating factors of AKI in patients with cirrhosis are
• Intravascular volume depletion due to overuse of diuretics, over-zealous use of lactulose or from gastrointestinal blood loss
• Bacterial infections
• Use of nephrotoxic drugs (non steroidal anti-inflammatory drugs, aminoglycosides, iodinated contrast media etc.)
# AKI-HRS diagnostic criteria
• ≥ Stage 2 AKI
• No improvement of serum creatinine after ≥48 h of diuretic withdrawal and volume expansion with albumin at a dose of 1 g/kg of body weight, up to a maximum of 100 g daily
• Absence of hypovolemic shock or infection that require vasoactive drugs to support blood pressure
• No current or recent use of nephrotoxic drugs
• Proteinuria <500 mg/day and haematuria <50 RBC/high power field
RRT: Renal replacement therapy
Rx: Prescription

## Management

- The management of AKI is largely supportive.
- This means patients require careful fluid balance to ensure that the kidneys are properly perfused but not excessively to avoid fluid overload.
- It is also important to review a patient's medication list to see what treatments may either be exacerbating their renal dysfunction or may be dangerous as a consequence of renal dysfunction.

The table below gives some examples of common drugs:

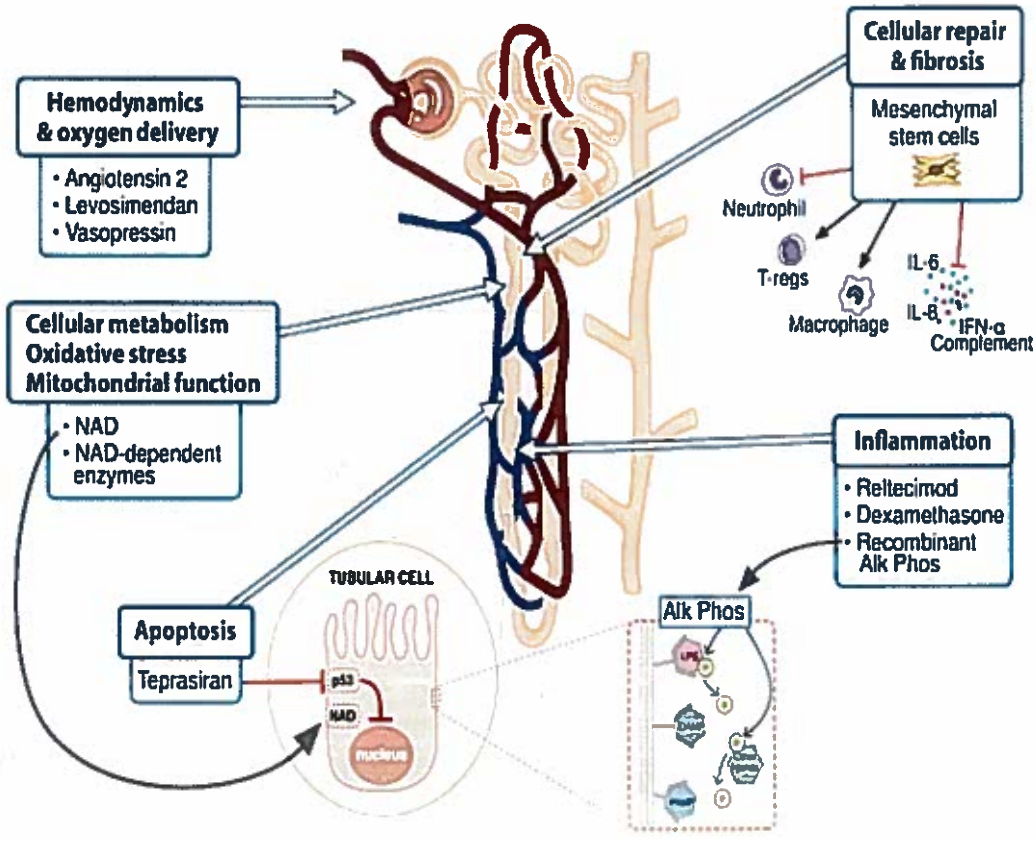
| Usually safe to continue in AKI | Should be stopped in AKI as may worsen renal function | May have to be stopped in AKI as increased risk of toxicity (but doesn't usually worsen AKI itself) |
|---|---|---|
| • Paracetamol<br>• Warfarin<br>• Statins<br>• Aspirin (at a cardioprotective dose of 75mg od)<br>• Clopidogrel<br>• Beta-blockers | • NSAIDs **(except if aspirin at cardiac dose e.g. 75mg od)**<br>• Aminoglycosides<br>• ACE inhibitors<br>• Angiotensin II receptor antagonists<br>• Diuretics | • Metformin<br>• Lithium<br>• Digoxin |

- Treatments which are **not recommend** include the routine use of loop diuretics (to artificially boost urine output) and low-dose dopamine (in an attempt to increase renal perfusion).
- There is however a role for loop diuretics in patients who experience significant fluid overload.
- **Hyperkalaemia** also needs prompt treatment to avoid arrhythmias which may potentially be life-threatening. The table below categorises the different treatments for **hyperkalaemia:**

| Stabilization of the cardiac membrane | Short-term shift in potassium from extracellular to intracellular fluid compartment | Removal of potassium from the body |
|---|---|---|
| • Intravenous calcium gluconate | • Combined insulin/dextrose infusion<br>• Nebulised salbutamol | • Calcium resonium (orally or enema)<br>• Loop diuretics<br>• Dialysis |

- Specialist input from a nephrologist is required for cases where the cause is not known or where the AKI is severe.
- All patients with suspected AKI secondary to urinary obstruction require prompt review by a urologist.
- Renal replacement therapy (e.g., hemodialysis) is used when a patient is not responding to medical treatment of complications, for example hyperkalaemia, pulmonary oedema, acidosis or uraemia.

## New drugs for acute kidney injury



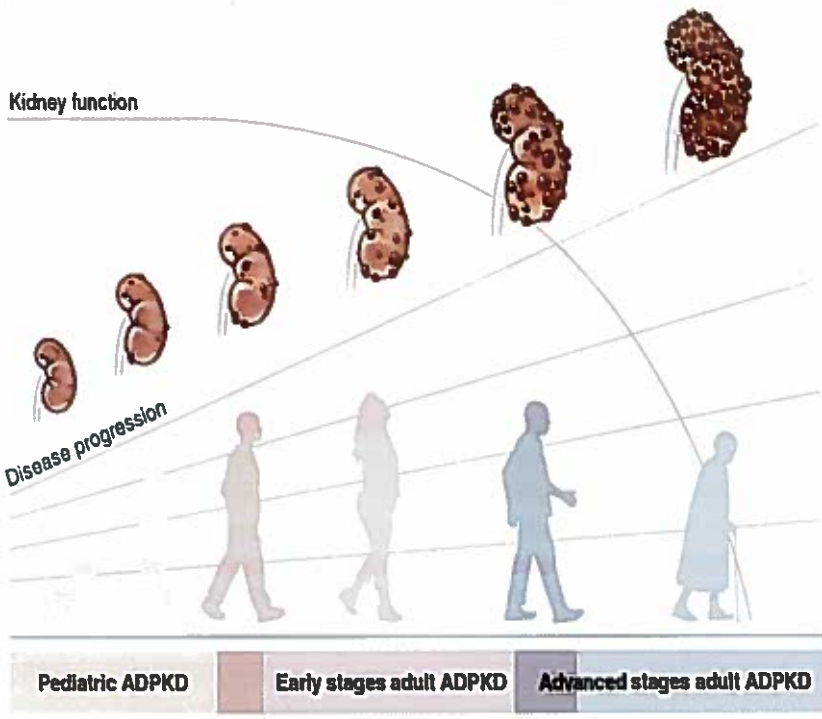

Selected compounds that impact known pathophysiological processes and have been studied in humans. Alk Phos: alkaline phosphatase; DAMP danger associated molecular pattern; IL interleukin; IFN-α interferon alpha; LPS lipopolysaccharide; NAD Nicotinamide adenine dinucleotide;T-regs regulatory T-cells; PAMP pathogen associated molecular pattern

# ADPKD (Autosomal dominant polycystic kidney disease)

- **Autosomal dominant** polycystic kidney disease **(ADPKD)** is the most common inherited cause of kidney disease, affecting 1 in 1,000 Caucasians.
- **So, offspring** of a parent with the disease have a **50% chance** of having the condition.
- The symptoms do **not** tend to **occur before the age of 40.**
- It is responsible for around 10% of the UK dialysis burden.
- Approximately **half** of patients with ADPKD will reach **ESRD** by the age of **60** and require renal replacement therapy.
- It is due to a mutation in the **PKD1 gene**.
- The PKD1 gene encodes for a **polycystin-1**, a large cell-surface glycoprotein of unknown function.
- Two disease loci have been identified, PKD1 and PKD2, which code for polycystin-1 and polycystin-2 respectively.
- **Genetic counselling** should be offered
- Regular follow up in renal clinic every 6 months

| ADPKD type 1 | ADPKD type 2 |
|---|---|
| **85%** of cases | 15% of cases |
| Chromosome **16** | Chromosome **4** |
| Presents with renal failure earlier | |

ADPKD type 1 = chromosome 16 = 85% of cases




| | | | |
|---|---|---|---|
| **Patient stratification** | • Very early onset, genetics, hypertension<br>• No available stratification scores | • Age, genetics, urological events, hypertension<br>• Stratification according to Mayo classification/PRO-PKD score | |
| **Current primary end points** | • Urine osmolarity | • Ht-TKV<br>• eGFR | • eGFR<br>• Ht-TKV |
| **Current secondary end points** | • Ht-TKV<br>• eGFR | • Urine osmolarity<br>• Number of cysts<br>• Copeptin | • Copeptin<br>• Liver cysts |
| **Potential end points** | • Texture/segmentation imaging<br>• Number of cysts<br>• Hypertension<br>• uMCP1<br>• PRO | • Texture/segmentation imaging/ liver cysts<br>• uMCP1/uEGF/suPAR/Kim-1/ β2 microglobulin/NGAL/ FGF23<br>• Urine-to-plasma urea ratio<br>• PRO/pain | • PRO/pain/QoL<br>• Liver cysts |
| **Future directions** | • "Bridging biomarkers": proteomic PKD score, microRNAs, and proteins in urinary extracellular vesicles | | • Prediction modeling |

Screening is recommended after 20 years age (if < 20 yrs. age >>>> Ultrasound gives false –ve result and CT is *not* needed as it will involve unnecessary high radiation dose to this young boy or girl, so just follow up US at the age of 20 years old age).
Cysts usually develop during teenage years, so one cannot be confident a child has not been affected until they are at least 20 years.
**A normal ultrasound scan at 20 years of age means you can be 90% confident** they are not affected, **a normal scan at 30 years increases the confidence level to 98%.**

Formal **screening for AKPD** occurs in early adulthood, usually with a renal **ultrasound** scan. Its sensitivity approaches **100% in those over 30 years**, but falls to less than 70% under this age.
For the diagnosis to be made there should be **at least two cysts in one or both** kidneys.
ADPKD is like a **CKD** with **high phosphate**, **low calcium** but with **normal/high Hb** due to excess erythropoietin secretion..

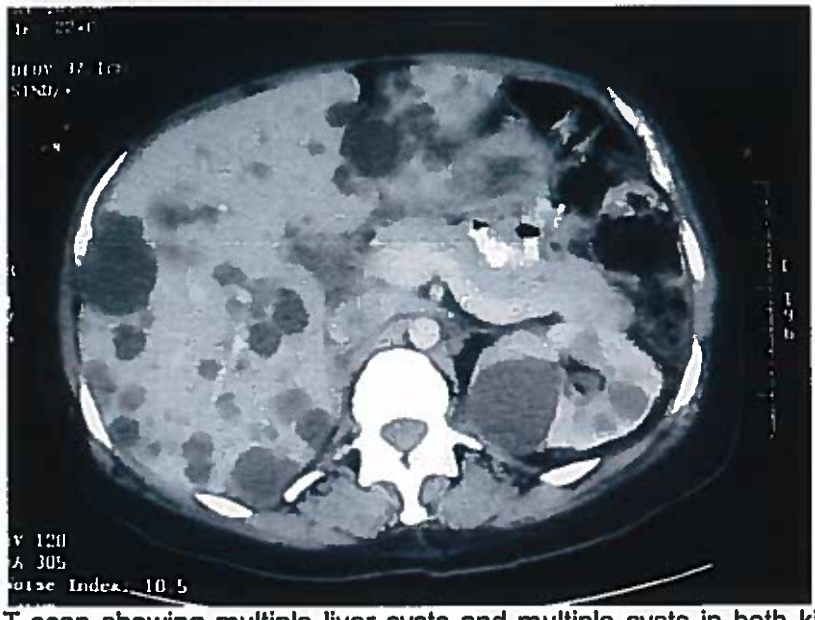
**The screening investigation** for relatives is **abdominal ultrasound**.

**Ultrasound diagnostic criteria (in patients with positive family history):**

- Two cysts, unilateral or bilateral, if aged < 30 years
- Two cysts in both kidneys if aged 30-59 years
- Four cysts in both kidneys if aged > 60 years

**CT is more sensitive than USS** and may aid in diagnosis in younger patients, especially below 20 years, but not used duo to radiation hazards

Polycystic kidneys in a 43-year-old woman with hematuria.



C T scan showing multiple liver cysts and multiple cysts in both kidneys in a patient with polycystic kidney disease.

- **MRI, for measuring Total kidney volume (TKV), and if increasing more than 5% YEARLY this indicates the use of vaptans (ANTI - ADH) to slow down the growing of the cysts.**
- **However, there are more criteria to fulfil in order to receive this drug as it was panned by FDA twice duo to serious side effect in form of sever liver injury, discussing the indications and criteria of using those drugs will follow later.**

**MRA angiography:** Current consensus is that screening for cerebral aneurysms should **only** be carried out in **high-risk patients**. These include factors such as:

- Previous rupture of aneurysm
- Concerning neurological symptoms (for example, severe headache)
- In patients with a family history of intracranial aneurysm.
- exposed to variations of atmospheric pressures like pilots,deep sea divers.
- those working with vibration tools - to screen for cerebral aneurysms.

Even if aneurysms are found, the rupture risk can still be low and the morbidity implications of curative surgery may outweigh conservative management especially if the aneurysm diameter is less than 7 mm.

## Prognostic tools besides imaging:

- The mutated gene (PKD1 is worse than PKD2).
- Male sex.
- Diagnosis before the age of 30 years.
- First episode of hematuria before age of 30 years.
- Onset of hypertension before age 35 years.
- Hyperlipidemia.
- Sickle cell trait.

**Associated conditions:**

- **Hypertension** (in over **75%** of cases).
- **Colonic diverticulae>>>>>>** screen by barium enema.
- Mitral valve prolapse **(MVP) in 25%** and **AR** >>>>> screen by echo.
- **Cerebral berry aneurysms** in 25% **>>> SAH >>> MRA** or CT angiography.
- Excessive **erythropoietin** production and polycythaemia.
- **Hepatic cysts** in **80%,** also involve the **pancreas** (10%), **ovaries (amenorrhea)** and spleen.

**Renal cell carcinoma with lung metastasis**: it is very rare but recognized complication of ADPCKD >>> **CT** Thorax & Abdomen

## Treatment:

- **ACEI** is the therapy of choice with Regular follow up of BP and renal function.
- **High fluid intake** (to prevent the formation of renal stones or blood clots) and to inhibit ADH which is responsible for increase of cyst size.
- **Loin pain** should be treated symptomatically.
- **Haematuria** should be treated conservatively except if the imaging is suspicious of underling malignancy or sever …at this stage injection of sclerosing material may be indicated and done by intervention radiologist.
- **UTIs** should be treated with lipophilic drugs (for example, ciprofloxacin, TMP_SM) as they have the best penetration into cyst fluid with prolonged duration time.

**For select patients, tolvaptan (vasopressin receptor 2 antagonist) may be an option. NICE recommended it as an option for treating ADPKD in adults to slow the progression of cyst development and renal insufficiency only if:**

- **they have chronic kidney disease stage 2 or 3 at the start of treatment**
- **there is evidence of rapidly progressing disease and**

- **the company provides it with the discount agreed in the patient access scheme.**

Extensive cysts are seen in an enlarged kidney

## ARPKD

Autosomal recessive polycystic kidney disease (ARPKD) is **much less common** than autosomal dominant disease (ADPKD). It is due to a **defect in a gene** located on **chromosome 6.**

**The autosomal recessive form is rare and usually causes death in childhood.**

Diagnosis may be made on **prenatal ultrasound** or **in early infancy** with abdominal masses and renal failure.

**Newborns** may also have features consistent with **Potter's syndrome secondary to oligohydramnios**.

End-stage renal failure develops in childhood. Patients also **typically have liver involvement**, for example portal and interlobular fibrosis.

Renal biopsy typically shows multiple **cylindrical** lesions at **right angles to the cortical surface.**

# Alport's syndrome

It is usually inherited in an **X-linked dominant (XLD)** pattern*.

Prevalence is **around 1 in 5000**, It is due to a defect in the gene which codes for type **IV** (4) collagen resulting in an abnormal glomerular-basement membrane **(GBM).**
The disease is more severe in **males** with females rarely developing renal failure.
**Deafness** usually occurs **before** the onset of renal failure, which is related itself to progressive nephritis.
Rigorous control of **hypertension** may delay the onset of **ESRD**, which is seen in **90%** of patients with Alport's **by the age of 40 years.** ☹

**90% of Alport's syndrome develop renal failure by the age of 40 years.**

*In around 85% of cases - 10-15% of cases are inherited in an autosomal recessive fashion with rare autosomal dominant variants existing.

Alport's syndrome - X-linked dominant **(XLD)** (in the majority)

Alport's syndrome - type **IV** 4 collagen defect

A favorite question is an Alport's patient with a failing renal transplant. This may be caused by the presence of anti-GBM antibodies **leading to a Goodpasture's syndrome like picture.**

**Alport's syndrome usually presents in childhood. The following features may be seen:**

- **Microscopic hematuria.**
- **Progressive renal failure.**
- **Bilateral sensorineural deafness.**
- **Ocular** abnormalities: **Lenticonus** (protrusion of the lens surface into the anterior chamber), **Corneal ulceration**, Corneal dystrophy, **Cataract, Retinitis pigmentosa.**
- Renal biopsy: **splitting of lamina densa seen on electron microscopy,** light microscopy may be unremarkable.
- lenticonus: protrusion of the lens surface into the anterior chamber

# Chronic kidney disease

## Causes

### Common causes of chronic kidney disease:

- Diabetic nephropathy
- Chronic glomerulonephritis
- Chronic pyelonephritis
- Hypertension
- Adult polycystic kidney disease.
- CKD of undetermined etiology (Mesoamerican nephropathy)

**Potential etiologies for Mesoamerican nephropathy in an immigrant dialysis population**

CJASN
Mesoamerican Nephropathy kidney failure n=52
Kidney failure from other causes n=63
Adjusted associations of agrochemical exposure with kidney failure due to Mesoamerican nephropathy
OR 1.33
(95% CI 1.12-1.58)
Agrochemical exposure for 1 year
OR 4.86
(95% CI 1.82-12.96)
Exposure to any agent
OR 12.25
(95% CI 1.51-99.38)
Exposure to paraquat
Compared to 16 case-matched healthy controls, exposure to paraquat or other agrochemicals was associated with Mesoamerican nephropathy kidney failure.
C57BL/6 mice n=73
10-15 weekly IP injections of paraquat or vehicle
Kidney failure and tubulointerstitial nephritis
No injury was observed in the lungs, liver, or spleen
OCT2 expression is higher in kidneys of male mice
Kidneys of male mice treated with paraquat displayed increased OCT2 expression and decreased MATE-1 expression
Conclusion Exposure to agrochemicals was associated with Mesoamerican nephropathy, and chronic exposure of mice to paraquat induced kidney failure similar to Mesoamerican nephropathy.

Michael W. Holliday Jr, Qingtian Li, Edlyn G. Bustamante, et al. Potential Mechanisms Involved in Chronic Kidney Disease of Unclear Etiology. CJASN doi: 10.2215/CJN.16831221.
Visual Abstract by Edgar Lerma, MD, FASN

## Risk factors associated with CKD progression in adults:

- cardiovascular disease
- proteinuria
- previous episode of acute kidney injury
- hypertension
- diabetes
- smoking
- African, African-Caribbean or Asian family origin
- chronic use of NSAIDs
- untreated urinary outflow tract obstruction.

CKD on haemodialysis - most likely cause of death is **IHD**

**Cardiovascular events account for 50% of the mortality in patients receiving dialysis.**

## eGFR and classification according to NICE guidelines 2021

**Chronic kidney disease CKD is defined as:**

**the presence of kidney damage or decreased kidney function (estimated glomerular filtration rate (eGFR) <60 ml/min per 1.73m2) for 3 or more months, irrespective of the cause. The persistence for at least 3 months is necessary to distinguish CKD from acute kidney injury (AKI).**

- **Serum Creatinine** may not provide an accurate estimate of renal function due to differences in muscle mass.
- For this reason, formulas were developed to help estimate the glomerular filtration rate (estimated GFR or eGFR) in stable chronic renal failure patients.
- **eGFR using creatinine** may be less reliable in certain situations (for example, acute kidney injury, pregnancy, edematous states, muscle wasting disorders, and in adults who are malnourished, who have higher muscle mass or use protein supplements, or who have had an amputation) and has not been well validated in certain ethnic groups (for example, black, Asian and other minority ethnic groups with CKD.
- Advise adults not to eat any meat in the 12 hours before having a blood test for eGFR creatinine. Avoid delaying the dispatch of blood samples to ensure that they are received and processed by the laboratory within 12 hours of venipuncture.

**NICE recommend** the use the Chronic Kidney Disease Epidemiology Collaboration **(CKD-EPI)** creatinine equation to estimate GFR creatinine for adults, using creatinine assays with calibration traceable to standardized reference material.

**KDIGO recommend** the use of Chronic Kidney Disease Epidemiology Collaboration **(CKD-EPI)** estimated glomerular filtration rate (eGFR) creatinine equation in adult patients with glomerular disease, and the **modified Schwartz equation** is preferred in children.

**The Full Age Spectrum (FAS) equation may be used in both adults and children (2021)**

GFR variables - **CAGE** - Creatinine, Age, Gender, Ethnicity

The guidelines recommend that age, gender, obesity without metabolic syndrome and ethnicity should **not** be used as risk markers to test people

**Offer testing for CKD using eGFR creatinine and ACR to adults with any of the following risk factors:**

- diabetes.
- hypertension.
- previous episode of acute kidney injury.
- cardiovascular disease (ischemic heart disease, chronic heart failure, peripheral vascular disease or cerebral vascular disease).
- structural renal tract disease, recurrent renal calculi or prostatic hypertrophy.
- multisystem diseases with potential kidney involvement, for example, systemic lupus erythematosus.
- gout.
- family history of end-stage renal disease (GFR category G5) or hereditary kidney disease.
- incidental detection of hematuria or proteinuria. [2021]

**Referral criteria:**

Refer adults with CKD for specialist assessment (taking into account their wishes and comorbidities) if they have any of the following:

- a 5-year risk of needing renal replacement therapy of greater than 5% (measured using the 4-variable Kidney Failure Risk Equation)
- an ACR of 70 mg/mmol or more, unless known to be caused by diabetes and already appropriately treated.
- an ACR of more than 30 mg/mmol (ACR category A3), together with hematuria
- a sustained decrease in eGFR of 25% or more and a change in eGFR category within 12 months.
- a sustained decrease in eGFR of 15 ml/min/1.73 m2 or more per year
- hypertension that remains poorly controlled (above the person's individual target) despite the use of at least 4 antihypertensive medicines at therapeutic doses.
- known or suspected rare or genetic causes of CKD.
- suspected renal artery stenosis. [2021]

**Detection of proteinuria:**

- use urine ACR rather than protein: creatinine ratio (PCR) because of the greater sensitivity for low levels of proteinuria.
- check an ACR between 3 mg/mmol and 70 mg/mmol in a subsequent early morning sample to confirm the result.

A repeat sample is not needed if the initial ACR is 70 mg/mmol or more. [2021].

Regard a confirmed ACR of 3 mg/mmol or more as clinically important proteinuria. [2021].

**Measure proteinuria with urine ACR in the following groups:**

- adults, children and young people with diabetes (type 1 or type 2).
- adults with an eGFR of less than 60 ml/min/1.73 m2.
- adults with an eGFR of 60 ml/min/1.73 m2 or more if there is a strong suspicion of CKD.
- children and young people without diabetes and with creatinine above the upper limit of the age-appropriate reference range.

**N.B: When ACR is 70 mg/mmol or more, PCR can be used as an alternative to ACR. [2021]**

## CKD CATEGORIES AND STAGES:

**Guide to Frequency of Monitoring (number of times per year) by GFR and Albuminuria Category**

| GFR categories (ml/min/1.73 m²) Description and range | | | | Persistent albuminuria categories Description and range | | |
|---|---|---|---|---|---|---|
| | | | | A1 | A2 | A3 |
| | | | | Normal to mildly increased | Moderately increased | Severely increased |
| | | | | <30 mg/g <3 mg/mmol | 30–300 mg/g 3–30 mg/mmol | >300 mg/g >30mg/mmol |
| | G1 | Normal or high | ≥90 | 1 if CKD | 1 | 2 |
| | G2 | Mildly decreased | 60–89 | 1 if CKD | 1 | 2 |
| | G3a | Mildly to moderately decreased | 45–59 | 1 | 2 | 3 |
| | G3b | Moderately to severely decreased | 30–44 | 2 | 3 | 3 |
| | G4 | Severely decreased | 15–29 | 3 | 3 | 4+ |
| | G5 | Kidney failure | <15 | 4+ | 4+ | 4+ |

**N.B:** Diagnosis of CKD stages 1 & 2 can be settled only if the patient has evidence of structural and /or functional derangement of the kidneys.
As GFR above 60 ml/min is considered normal if, and only if the patient has no abovementioned derangements.

- **Chronic kidney disease especially stages I & II is only diagnosed if:** supporting tests such as urinalysis or renal ultrasound are abnormal with the reduced GFR (i.e., not only with reduced eGFR accompanied with normal urinalysis or renal ultrasound).

- (Ex. Pt. with eGFR 60 ml/min and normal U&E, urine analysis and Abd u/s **HAS** no CKD)
- **The eGFR is often inaccurate in people with extremes of muscle mass. Body builders often have an inappropriately low eGFR.**

## Hypertension in CKD

### Please refer to KDIGO guidelines and NICE guidelines on hypertension in CKD 2021

- **NICE's guideline on hypertension in adults recommends** using clinic blood pressure for monitoring response to lifestyle changes or medical treatment, aim for a clinic **systolic blood pressure below 140 mmHg** (target range 120 to 139 mmHg) and a clinic **diastolic blood pressure below 90 mmHg** [2021].
- In adults with CKD and an ACR of 70 mg/mmol or more, aim for a clinic systolic blood pressure below 130 mmHg (target range 120 to 129 mmHg) and a clinic diastolic blood pressure below 80 mmHg. [2021].
- In children and young people with CKD and an ACR of 70 mg/mol or more, aim for a clinic systolic blood pressure below the 50th percentile for height. [2021]
- Offer an angiotensin-receptor blocker (ARB) or an angiotensin-converting enzyme (ACE) inhibitor (titrated to the highest licensed dose that the person can tolerate) to adults, children and young people with CKD who have hypertension and an ACR over 30 mg/mmol (ACR category A3 or above). [2021].
- For adults with CKD and diabetes (type 1 or type 2) offer an ARB or an ACE inhibitor (titrated to the highest licensed dose that the person can tolerate) if ACR is 3 mg/mmol or more. [2021]
- **NICE are reviewing the evidence on SGLT2 inhibitors in people with CKD and type 2 diabetes, and we may update recommendations as a result of this. The consultation on this review is scheduled to begin on 1 September 2021, and the review will publish in November 2022.**
- For adults with CKD and type 2 diabetes, offer an SGLT2 inhibitor, in addition to an ARB or an ACE inhibitor at an optimized dose if:
- ACR is more than 30 mg/mmol, and Chronic kidney disease they meet the criteria in the marketing authorization (including relevant eGFR thresholds). Monitor for volume depletion and eGFR decline.
- In August 2021, not all SGLT2 inhibitors were licensed for this indication.
- For adults with CKD but without diabetes:

- refer for nephrology assessment and offer an ARB or an ACE inhibitor (titrated to the highest licensed dose that they can tolerate).
- **Do not offer** a combination of renin–angiotensin system antagonists to adults WITH ACE inhibitors. Explain to adults with CKD (and their family members or carers, as appropriate) who are prescribed renin–angiotensin system antagonists about the importance of:
- achieving the optimal tolerated dose of renin–angiotensin system antagonists and
- monitoring eGFR and serum potassium in achieving this safely.
- Measure serum potassium concentrations and estimate the GFR before starting renin–angiotensin system antagonists in people with CKD. Repeat these measurements between 1 and 2 weeks after starting renin–angiotensin system antagonists and after each dose increase.
- Do not routinely offer a renin–angiotensin system antagonist to adults with CKD if their pre-treatment serum potassium concentration is greater than 5.0 mmol/litre.

If an adult cannot use renin–angiotensin system antagonists because of hyperkalemia:

- assess for and treat any other factors that promote hyperkalemia and
- recheck serum potassium concentration.

Be aware that more frequent monitoring of serum potassium concentration may be needed if medicines known to promote hyperkalemia are prescribed for use in people alongside renin–angiotensin system antagonists.

Stop renin–angiotensin system antagonists in adults if the serum potassium concentration increases to 6.0 mmol/litre or more and other medicines known to promote hyperkalemia have been discontinued.

**Use sodium zirconium cyclosilicate and patiromer to reduce potassium level [2021]**

After introducing or increasing the dose of renin–angiotensin system antagonists in adults, do not modify the dose if either:

- the GFR decrease from pretreatment baseline is less than 25% or
- the serum creatinine increase from baseline is less than 30%.

If there is a decrease in eGFR or increase in serum creatinine after starting or increasing the dose of renin–angiotensin system antagonists, but it is less than 25% (eGFR) or 30% (serum creatinine) of baseline, repeat the test in 1 to 2 weeks. Do not modify the renin–angiotensin system antagonist dose if

the change in eGFR is less than 25% or the change in serum creatinine is less than 30%.

If an adult's eGFR change is 25% or more, or the change in serum creatinine is 30% or more:

- investigate other causes of a deterioration in kidney function, such as volume depletion or concurrent medication (for example, NSAIDs)
- if no other cause for the deterioration in kidney function is found, stop the renin–angiotensin system antagonist or reduce the dose to a previously tolerated lower dose, and add an alternative antihypertensive medication if needed The majority of patients with CKD will require more than 2 drugs to treat HTN.

**ACE inhibitors:**

- They are first line and are particularly helpful in proteinuric renal disease (e.g., diabetic nephropathy).
- As these drugs tend to reduce filtration pressure a small fall in glomerular filtration pressure (GFR) and rise in creatinine can be expected.

**Furosemide:**

- It is useful as an anti-hypertensive in patients with CKD, **particularly when the GFR falls to below 45 ml/min*.**
- It has the added benefit of lowering serum potassium.
- High doses are usually required, the needed dose to achieve diuresis is roughly estimated by role of 20
  (20*creatinine = required dose of frusemide)
- If the patient becomes at risk of dehydration (e.g., Gastroenteritis) then consideration should be given to temporarily stopping the drug.

## Renal vascular disease

Renal artery stenosis secondary to atherosclerosis accounts for around 90% of renal vascular disease, with fibromuscular dysplasia being the most common cause of the remaining 10%. FMD is more common in young women 30-40 years and characteristically has a 'string of beads' appearance on angiography. Patients respond well to balloon angioplasty.

### 1-fibromuscular dysplasia

#### Epidemiology

- 90% of patients are female

#### Features

- hypertension
- chronic kidney disease or more acute renal failure e.g. **secondary to ACE-inhibitor initiation**
- 'flash' pulmonary oedema

### 2-Atherosclerotic renal artery stenosis.

It is associated with risk factors such as smoking and hypertension that cause atheroma elsewhere in the body.
It may present as hypertension, chronic renal failure or 'flash' pulmonary oedema.
In 30% of cases the disease is bilateral.
Limb arteries with PVD can be affected by fibromuscular dysplasia, but this occurs only in about 5% of cases.

**Arteriosclerosis (renal artery sclerosis)** is a more common cause of RAS than fibromuscular dysplasia.
**40%** may have **peripheral vascular disease (PVD)** with **intermittent claudication** and there may be **proteinuria**.

## Investigation:

- **MRA** (MR angiography) is now the investigation of choice.
- CT angiography.
- Conventional renal angiography is less commonly performed used nowadays, but may still have a role when planning surgery.

**MR angiography (MRA)** should be considered the optimum non-invasive screening test for renovascular disease, and **can be performed safely in patients with CKD stage 3 and 4.**
However, there is increasing concern regarding gadolinium related nephrogenic systemic fibrosis (NSF) and guidelines may therefore change in the future.

**Flash pulmonary oedema, U&Es worse on ACEIs, Asymmetrical kidneys >>>>>>→**
**Renal artery stenosis (RAS)** >>>>>> Do **(MRA)** MR angiography

Summary of Imaging modalities Used to Diagnose Atherosclerotic Renovascular Disease

| Imaging Modality | Sensitivity | Specificity | Strengths | Limitations |
|---|---|---|---|---|
| Duplex ultrasound | 91% 100% | 82% 91% | Inexpensive, noninvasive, provides waveform and Velocity data provides data about Kidney viability (resistive index) | Operator dependent, limited by high BM limited availability in some countries |
| Multidetector CTA | 64% 96% | 90% 92% | Rapid multiplanar acquisition, allows detection of accessory renal arteries | low/moderate levels of radiation, requires iodinated contrast |
| MRA | 94% 97% | 85% 93% | NO radiation or iodinated contrast required | long acquisition times (-1h), may overestimate degree of stenosis |
| Calheler angiography | 100% 100% | | Gold standard of renal artery evaluation, enables measurement of pre-and postintervention gradients, can evaluate and treat in same setting | invasive procedure, only 2D planar Images acquired, ideally requires iodinated contras (CO2 can be substituted with lesser resolution |

## Treatment:

- Stop ACEIs.
- Non-ACEI control of BP like CCBs.
- Start **Aspirin** and **statin**.
- Renal artery revascularization in certain cases.

**Box 1.** KDIGO Consensus on Indications and Nonindications for Renal Artery Revascularization in Atherosclerotic Renovascular Disease

### Definite indications

- Acute pulmonary edema or acute decompensations of heart failure and high-grade RAS[96]
- Progressive CKD in high-grade (>75%) RAS (bilateral or solitary kidney)[21]
- AKI due to acute renal artery occlusion or high-grade RAS[83]
- ACEi or ARB intolerance in high-grade RAS
- Kidney transplant with RAS (symptomatic or asymptomatic)[91]

### Possible indications

- Chronic heart failure and high-grade RAS[31,73]
- Coexistence of progressive CKD and uncontrolled hypertension[21,84]
- Asymptomatic high-grade RAS (either bilateral or supplying solitary kidney) with viable renal parenchyma (to prevent atrophy)
- New (<3 mo) dialysis patient with nonfunctioning but possibly viable kidney[53-55,83,84]

### Nonindications

- Moderate to severe hypertension alone
- Asymptomatic unilateral or bilateral (<75%) RAS[63,70,71]

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; AKI, acute kidney injury; ARB, angiotensin receptor blocker; KDIGO, Kidney Disease: Improving Global Outcomes; RAS, renal artery stenosis. Adapted from Johansen et al[1] with permission of the copyright holder; original content ©2021 International Society of Nephrology.

Renal artery stenosis (RAS) **is a potential cause of hypertension.**
Typically patients are vasculopaths and **poor prognosis (80% mortality at five years)** is related to concurrent coronary disease.
It is almost exclusively caused by atherosclerosis, but other causes include fibromuscular dysplasia, vasculitis and external compression.
Typical ultrasound changes are **asymmetrical kidneys**; the affected kidney **>2 cm smaller** than the unaffected kidney.
**ACE inhibitors are contraindicated** in renal artery stenosis as they inhibit the contraction of the efferent arterioles which promote glomerular filtration in the disease.

**NB:** A rise in creatinine of 15% from baseline is expected with commencement of a ACEIs. A large rise in creatinine > 20% should warrant a search for renal artery stenosis (RAS) given the likelihood of vascular disease.

**NB:** The association of **"flash" pulmonary oedema** and **hypertension** in a **young** patient **(< 50 years)** with **no obvious cardiovascular** risk factors >>>> points towards **fibromuscular dysplasia** >>> Treatment: **Angioplasty.**
In pulmonary oedema patients can cough up **frothy pink sputum.**

**EX: Young female 30** years old with **sudden onset breathlessness** while eating dinner with cough and **frothy pink sputum** with **high BP 160/100** mmHg >>> flash pulmonary oedema with? **Fibromuscular dysplasia.**

**Congenital RAS** is extremely rare and may be associated with **coarctation of the aorta.**

**NB:** When ACEI is started, **non-progressive rise in creatinine of 20-30% is acceptable, but** a **progressive** rise of creatinine **> 30%** should prompt consideration of **RAS.**
Guidelines generally suggests **checking** serum creatinine **1 week, 1 month** and **then periodically** after starting ACEIs

# Parenthood With Kidney Failure: Answering Questions Patients Ask About Pregnancy

ISN INTERNATIONAL SOCIETY OF NEPHROLOGY

## Delivery rates in women receiving hemodialysis

Increased from 2.1 to 3.6/1000 patient-yrs. (2002 to 2015 USRD)

## Preparing for a Pregnancy

Maternal health should be optimized across a range of domains: medication exposures, correction of anemia, control of infection, smoking cessation, blood pressure, blood sugar and updated vaccination.

## Should I Have a Baby?

Important role of dedicated counselling and shared decision to reflect patients' values and preferences, clinical context and complexity, the level of risk they are willing to accept, with the level of autonomy they desire.

## When is the Best Time for Me to Have a Baby?

The optimal "window" for pregnancy reflects biological factors (age, CKD stage, likelihood and timing of transplantation, comorbidities, and potential fertility) and social factors and individual context.

## What Happens If I Have an Unexpected Pregnancy?

Decision-making around continuation of an unplanned pregnancy depends on the gestational age, potential teratogenic exposures, risks of miscarriage, risk of proceeding with pregnancy, and patient preferences.

## Men With Kidney Failure

- Uremic environment effect has detrimental effects on male sex hormones , erectile function, sperm quality, and fertility.
- Men receiving kidney replacement therapy do successfully father children with excellent outcomes.

## Timing of pregnancy for transplant recipients

Minimum 1 to 2 yrs. post-transplant for lower risk of rejection and infection, switch to nonteratogenic drugs and optimization of overall health

## Will Pregnancy Be Dangerous for Me or My Baby?

Women with kidney failure have 2- to 10-fold risk of adverse maternal-fetal outcomes

*USRD: United States Renal Data System

### Birth rates Transplanted women

Around 72% to 93%, similar to or higher than that observed in the general population, but early pregnancy loss remains high

### Acute rejection during pregnancy

Reported in 1% to 10% of pregnancies

### Mode of delivery

Based on obstetrical reasons

### Breastfeeding

True contraindications are extremely rare, and benefits outweigh the minimal risk

CKD: Chronic kidney disease

KI REPORTS
Kidney International Reports

Jesudason S et al, 2022

# Chronic kidney disease: proteinuria

- **Proteinuria** is an important marker of CKD, especially for diabetic nephropathy.
- NICE recommend using the albumin: creatinine ratio (**ACR**) in preference to the protein: creatinine ratio (PCR) when identifying patients with proteinuria as it has greater sensitivity.
- **For quantification and monitoring of proteinuria, PCR** can be used as alternative follow up parameter, although ACR is recommended in diabetics.
- Urine reagent strips are not recommended unless they express the result as an ACR.

## Approximate equivalent values:

| ACR (mg/mmol) | PCR (mg/mmol) | Urinary protein excretion (g/24 h) |
|---|---|---|
| **30** | **50** | **0.5** |
| **70** | **100** | **1** |

Average individuals pass around 10mmol urinary creatinine each day. Therefore:

- U PCR **50** = **500mg** protein/day
- U PCR **100** = **1000mg** protein/day

So, a 24hour urinary protein collection of **1g** is therefore approximately equivalent to **urinary PCR of 100 mg/mmol**.

### Collecting an ACR sample:

- By collecting **a 'spot' sample** it avoids the need to collect urine over a 24hour period in order to detect or quantify proteinuria.
- Should be **a first-pass morning** urine specimen.
- If the initial ACR is greater than **30** mg/mmol and less than **70** mg/mmol, **confirm** by a subsequent early morning sample.
- If the initial ACR is greater than **70** mg/mmol a repeat sample need **not** be tested.

### Interpreting the ACR results:

- In **non-diabetics** an ACR greater than **30** mg/mmol is considered clinically significant proteinuria.
- In **diabetics** microalbuminuria (ACR greater than 2.5 mg/mmol in men and ACR greater than **3.5** mg/mmol in **women**) is considered clinically significant.

## Frequency of monitoring eGFR (number of times per year by eGFR and ACR categories) for people with or at risk of CKD

| eGFR categories (mL/min/1.73 m2) | ACR categories (mg/mmol) | | |
|---|---|---|---|
| | **A1 (< 3) Normal to mildly increased** | **A2 (3-30) Moderately increased** | **A3 (> 30) Severely increased** |
| G1 >=90 Normal and high | =< 1 | 1 | >= 1 |
| G2 60-89 Mild reduction related to normal range for a young adult | =< 1 | 1 | >= 1 |
| G3a 45-59 Mild to moderate reduction | 1 | 1 | 2 |
| G3b 30-44 Moderate to severe reduction | =< 2 | 2 | >= 2 |
| G4 15-29 Severe reduction | 2 | 2 | 3 |
| G5 <15 Kidney failure | 4 | >=4 | >=4 |

## Management

- ACE inhibitors (or angiotensin II receptor blockers) are key in the management of proteinuria
  - they should be used first-line in patients with coexistent hypertension and CKD, if the ACR is > 30 mg/mmol
  - if the ACR > 70 mg/mmol they are indicated regardless of the patient's blood pressure

**NB: Newly detected microalbuminuria** in **IDDM** Pt. >>>>> should be **confirmed** by **repeat test 3-6 months** period before starting treatment with ACEI/ARBs.

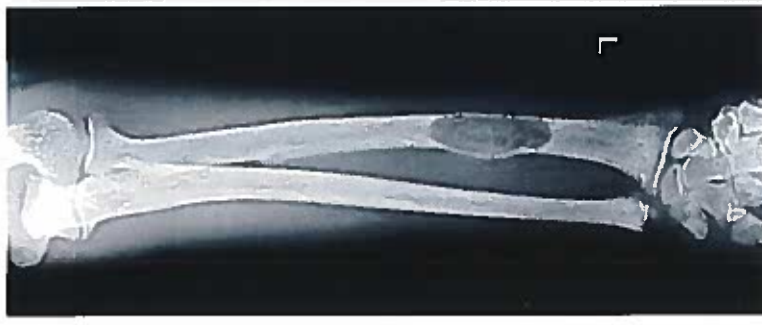
# Chronic kidney disease: bone disease

## Basic problems in chronic kidney disease:

- **Low vitamin D** (1-alpha hydroxylation normally occurs in the kidneys).
- **High phosphate:** due to **decreased renal excretion.**
- **Low calcium**: due to lack of vitamin D, high phosphate.
- **Secondary hyperparathyroidism**: due to low calcium, high phosphate and low vitamin D.

## Several clinical manifestations may result:

- **Osteitis fibrosa cystica**: called hyper-parathyroid bone disease, which can cause brown tumor.
- **Adynamic bone disease**:
  a. reduction in cellular activity (both osteoblasts and osteoclasts) in bone
  b. may be due to over treatment with vitamin D
- **Osteomalacia**: due to low vitamin D
- Osteoporosis
- Osteosclerosis



**X-ray of a Brown tumor caused by secondary hyperparathyroidism in a young female with chronic kidney disease**

The healthy adult kidney excretes **5400 mg per week** of **phosphate**.

**Dialysis** is able to remove **only** about **half** of the phosphate that the healthy kidney would be able to do.

So the maximum amount of phosphate that can be removed by dialysis in a patient with anuric renal failure who is dialysis dependent is **2700 mg / week.**

# CKD - ANAEMIA AND Erythropoietin (EPO)

- Erythropoietin is a haematopoietic growth factor that stimulates the production of erythrocytes.
- The main uses of erythropoietin are to treat the anaemia associated with chronic kidney disease and that associated with cytotoxic therapy.
- Erythropoietin treats CKD associated anaemia which in turn would **improve exercise tolerance.**
- **It does not improve renal function.**

## Side-effects of erythropoietin:

- **Hypertension - 20%** of patients require increased antihypertensive medications. It may even **precipitate a hypertensive crisis**.it should be avoided until BP is better controlled below 170/110 mmHg.
- **Encephalopathy** and **seizures (EPO-induced epilepsy)**: it is **rare** adverse event and can be seen **within 90 days** of EPO initiation.
- **Hyperkalaemia**
- Bone aches
- Flu-like symptoms
- **Anaphylaxis**: skin rashes, urticaria
- **Pure red cell aplasia**: is a rare unwanted effect due to stimulation of antibodies by administered EPO which cross reacts with the patient's endogenous EPO, this risk is greatly reduced with darbepoetin.
- Raised PCV increases risk of **thrombosis** (e.g. Fistula)
- A dose-dependent **rise in platelet count** is common, due to erythropoietin affinity for thrombopoietin receptors.
- Iron deficiency 2nd to increased erythropoiesis.

**NB**: Erythropoiesis-stimulating agents act as a growth factor in the context of **active malignancy**, and this increases the mortality of patients with malignancy (e.g. renal cell carcinoma) who receive erythropoietin. The other major risk factor associated with these drugs is **ischaemic stroke**.

There are a number of reasons why patients may fail to respond to erythropoietin therapy:

- Iron deficiency
- Inadequate dose
- Concurrent infection/inflammation
- Hyperparathyroidism
- bone disease
- Aluminum toxicity

**Before** initiation of recombinant erythropoiesis-stimulating agents the patient should be **iron replete by IV iron** till **ferritin** is restored to mid-range **> 100** µg/L and **transferrin saturation >20%** with normal vitamin B12 and folate.

Oral iron is therapy usually ineffective, so **IV iron therapy** is required.

Use percentage of hypochromic red blood cells (% HRC; more than 6%), but only if processing of blood sample is possible within 6 hours.

- If using percentage of hypochromic red blood cells is not possible, use reticulocyte Hb content (CHr; less than 29 pg) or equivalent tests – for example, reticulocyte Hb equivalent.

Offer iron therapy to adults, children and young people with anemia of CKD

who are receiving ESAs to achieve:

- percentage of hypochromic red blood cells less than 6% (unless ferritin is greater than 800 micrograms/liter)
- reticulocyte Hb count or equivalent tests above 29 pg (unless serum ferritin is greater than 800 micrograms/liter).
- If these tests are not available or the person has thalassaemia or thalassaemia trait, use a combination of transferrin saturation (less than 20%) and serum ferritin

Blood transfusion should be avoided if possible as patient is fluid overloaded and it may precipitate pulmonary oedema.

Where possible blood transfusion should be avoided in patients who may be candidates for transplantation as the development of antibodies to alloantigen may make future transplantation more problematic.

The **serum ferritin** and **transferrin saturation** should be checked, as most patients will be iron deficient.

Do not prescribe supplements of vitamin C, folic acid or carnitine as adjuvants

specifically for the treatment of anemia of CKD

**Targets for treatment for anemia in CKD patients are:**

- **Hemoglobin 10-12 g/dl** (European renal guideline, target Hb **11** g/dl).
- **Ferritin: >100 µg/L** in pre-dialysis and peritoneal dialysis patients, **>200** µg/L in hemodialysis patients
- **Transferrin saturation >20%**

**Transferrin saturation (Fe/TIBC): <20%** should be considered a marker of functional iron deficiency when the ferritin is >100 µg/L.

Where patients have absolute iron deficiency **oral** iron supplementation may be adequate. However, where there is functional iron deficiency, **IV** iron replacement is recommended.

Do not check iron levels earlier than 1 week after administering intravenous iron in adults, children and young people with anaemia of CKD. The length of time to monitoring of iron status is dependent on the product used and the amount of iron given.

EPO abuse in **sports**: It can be detected in **urine** for a **few weeks** following the most recent injection

**Oral bicarbonate supplements in the management of metabolic acidosis:**

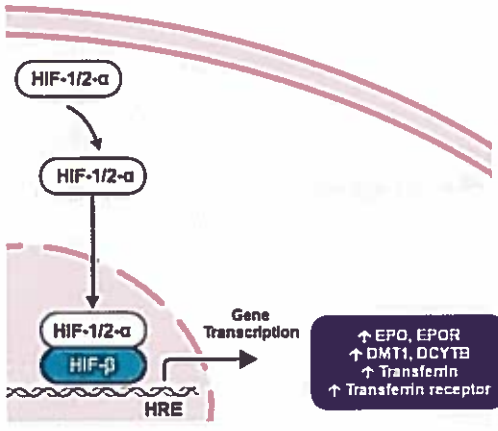
Detailed advice on the management of metabolic acidosis is beyond the scope of this guideline. If uncertain, seek advice from your local renal service.

Consider oral sodium bicarbonate supplementation for adults with both:

- a GFR less than 30 ml/min/1.73 m (GFR category G4 or G5) and
- a serum bicarbonate concentration of less than 20 mmol/litre.

# New treatment of dialysis associated anemia (HIF=HYPOXIA INDUCING FACTOR)

## Hypoxia




**Under hypoxia**

Hydroxylation of alpha subunits inhibited, stabilizing the HIF-α subunits

↓

Stabilized HIF-α translocate to the nucleus & bind to HIF-β

↓

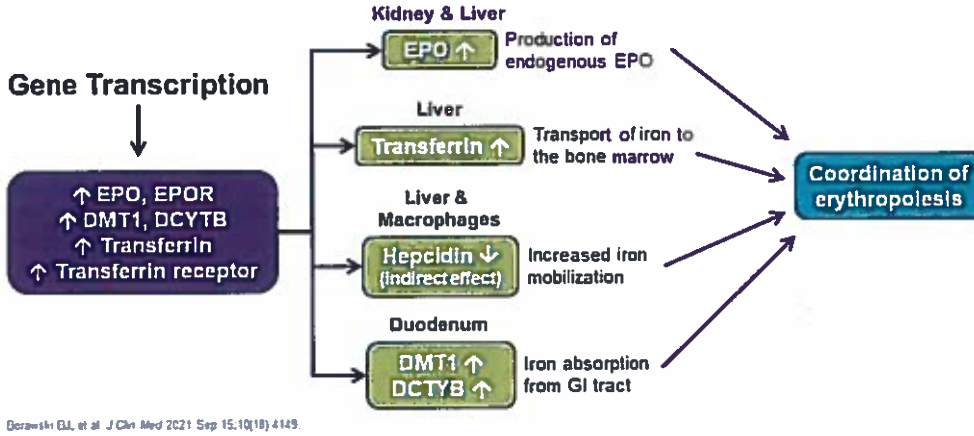
HIFs, together with other cofactors, bind hypoxia response elements (HREs)

↓

**Gene Transcription**

Watts D et al Int J Mol Sci 2020 Oct 30 21(21) 8131 Vaa A et al Cells 2020 Apr 16 9(4) 992

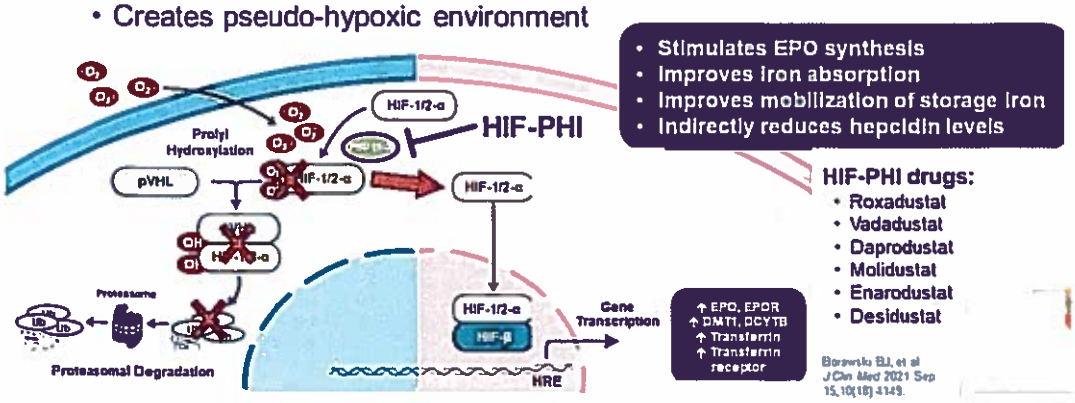
## Hypoxia




Berawski BJ, et al J Clin Med 2021 Sep 15;10(18):4149.

# New Drug Class: HIF-PHIs

- **Inhibition of PHD prevents the degradation of HIF-α**
  - Creates pseudo-hypoxic environment




## Calciphylaxis

- Calciphylaxis is a rare complication of end-stage renal failure.
- The underlying mechanism is not clear, however it results in deposition of calcium within arterioles causing microvascular occlusion and necrosis of the supplied tissue.
- It most commonly affects the skin and **presents with painful necrotic skin lesions.**
- The risk of developing calciphylaxis is linked with hypercalcemia, hyperphophatemia and hyperparathyroidism.
- Warfarin is widely reported as causing/exacerbating calciphylaxis in high risk patients, however the underlying mechanism is not known.

**Treatment** of calciphylaxis focuses on reducing calcium and phosphate levels, controlling hyperparathyroidism and avoiding contributing drugs such as warfarin and calcium containing compounds.
Sodium thiosulfate treatment is effective in mild to moderate cases.

## Prescribing in patients with renal failure

Questions regarding which drugs to avoid in renal failure are common.

### Drugs to avoid in renal failure:

- Antibiotics: tetracycline, nitrofurantoin
- NSAIDs
- Lithium
- Metformin

**Drugs likely to accumulate in chronic kidney disease - need dose adjustment:**

- Most antibiotics including penicillin, cephalosporins, vancomycin, gentamicin, streptomycin
- Digoxin
- Atenolol
- Methotrexate
- Sulphonylurea
- Furosemide
- Opioids

**Drugs relatively safe - can sometimes use normal dose depending on the degree of chronic kidney disease:**

- Antibiotics: Ceftriaxone, Erythromycin, Doxycycline, Rifampicin, Clindamycin, Linezolid.
- Diazepam
- Warfarin

## Renal transplantation

The human leucocyte antigen (**HLA**) system is the name given to the major histocompatibility complex (**MHC**) in humans.
It is coded for on chromosome **6**.

### Some basic points on the HLA system:

- Class 1 antigens include A, B and C.
- Class 2 antigens include DP, DQ and DR.
- when HLA matching for a renal transplant the relative importance of the HLA antigens are as follows DR > B > A

Renal transplant HLA matching - **DR** is the most important

### Transplants are classified as:

- **Autografts**: in which the **same individual** acts as both donor and recipient.
- **Isografts**: in which the donor and recipient are genetically identical (**twins**).
- **Allografts**: where the donor and recipient are genetically dissimilar but belong to the same species **(the commonest).**

- **Xenografts**: in which the donor and recipient belong to different species (between animal and human).

In **orthotopic** transplants: the transplanted part is placed in its normal anatomical location.
In **heterotopic** transplants: it is placed in different anatomical location.

## Graft survival:

- For cadaveric transplants: 1 year = 90%, 10 years = 60%
- For living-donor transplants: 1 year = **95%**, 10 years = **70%**

## Post-op problems:

- ATN of graft
- Vascular thrombosis
- Urine leakage
- UTI

**Technical complications**

| Complication | Presenting features | Treatment |
|---|---|---|
| Renal artery thrombosis | Sudden complete loss of urine output | Immediate surgery may salvage the graft, delays beyond 30 minutes are associated with a high rate of graft loss |
| Renal artery stenosis | Uncontrolled hypertension, allograft dysfunction and oedema | Angioplasty is the treatment of choice |
| Renal vein thrombosis | Pain and swelling over the graft site, haematuria and oliguria | The graft is usually lost |
| Urine leaks | Diminished urine output, rising creatinine, fever and abdominal pain | USS shows perigraft collection, necrosis of ureter tip is the commonest cause and the anastomosis may need revision |
| Lymphocele | Common complication (occurs in 15%), may present as a mass, if large may compress ureter | May be drained with percutaneous technique and sclerotherapy, or intraperitoneal drainage |

## Hyperacute acute rejection (minutes to hours):

- Due to **pre-existent antibodies** against donor HLA type 1 antigens (a **type II** hypersensitivity reaction) and is therefore **IgG** mediated.
- Rarely seen due to HLA matching.

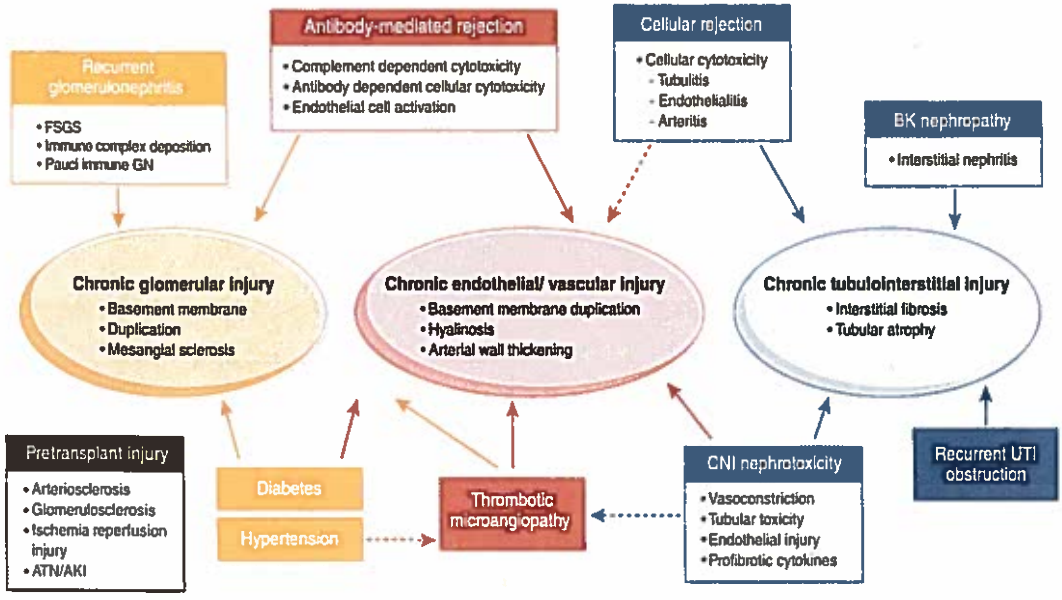
## Acute graft failure (< 6 months):

- Acute rejection develops in **30-50%** of renal transplant recipient, the risk is greater up to 2 weeks post-operatively.
- The risk is greater in the first 3 weeks after transplant.
- Usually due to **mismatched HLA Cell-mediated (cytotoxic T cells).**
- May be reversible with steroids and immunosuppressant.
- Other causes include:
  1) **Cytomegalovirus** infection.
  2) Cyclosporine toxicity (acute or chronic): drug-drug interaction especially with enzyme inhibitors like azithromycin.
  3) ATN of the graft.
  4) Vascular thrombosis.
  5) Ureteric leakage from the anastomosis.

**Cytomegalovirus (CMV)** is the most common and important viral infection in solid organ transplant recipients >>> **Ganciclovir** is the treatment of choice.

## Chronic graft failure (> 6 months):

- The pathogenesis of chronic rejection is **not clear**; some prefer the term "chronic allograft nephropathy" (CAN) since both **immunological** (antigen-dependent and antigen-independent) and **non-immunological** factors have been identified.
- **Both** antibody and cell mediated mechanisms cause fibrosis to the transplanted kidney (chronic allograft nephropathy) (CAN).
- Recurrence of **original** renal disease (**MCGN > IgA > FSGS**).
- Risk factors include:
  - Number of previous acute rejection episodes
  - Presence of **anti-HLA antibodies**
  - Anti-endothelial antibodies
  - CMV infection
  - Hypertension
  - Dyslipidemia
  - Functional mass of the donor kidney, and
  - Delayed graft function (a clinical manifestation of ischemia/reperfusion injury).




Schema of the potential sites of injury associated with late allograft failure. There may be "fixed" injury as a consequence of the donation and transplant process ("pretransplant injury"). Three target sites of injury within the kidney are shown, with defined histologic characteristics. The entities that contribute to these sites directly (solid arrows) are shown aligned to their injury at that site. There may also be "crosstalk" of disease processes between compartments (hashed arrows) as well as cumulative injury from multiple entities directly (solid arrows) or indirectly (hashed arrows). ATN, acute tubular necrosis; CNI, calcineurin inhibitor; UTI, urinary tract infection.

## Graft versus host disease (GVHD):

GVHD occurs when **donor lymphocytes** engraft in a susceptible recipient.
Products implicated in cases of transfusion associated (TA)-GVHD include: ☹

- Non-irradiated whole blood
- Packed red blood cells
- Platelets
- Fresh non-frozen plasma.
- Granulocytes

**The following have not been implicated:** ☺

- **Frozen** deglycerolized red blood cells
- **FFP** and
- **Cryoprecipitate.**

In renal transplant there is an increased risk of GVHD, hence **irradiated blood** is indicated.

**NB:** Leukocyte depleted blood is already the standard of care in the UK.

### Recurrence of renal pathologies post-renal transplantation:

1) **Membranoproliferative GN: 40-90%** recurrence rate, type 2 much greater than type 1).
2) FSGS: 40%.
3) Membranous GN: 30%.

### CMV infection post-renal transplantation:

It is very likely that the transplanted kidney has come from a **CMV positive donor.**

Symptoms of CMV infection post transplantation can appear **anytime from 6-60 days after surgery**, and are characterized by **pyrexia**, **flu** like symptoms or an **infectious mononucleosis** type picture (sore throat and pharyngitis).

treatment: **IV Ganciclovir.**

Kidney transplant recipients have a high risk of developing **non-melanoma skin cancer,** so cancer surveillance is an important consideration in kidney transplant recipients.

The patient may has a **malignant melanoma** with **liver metastases**, hence the deranged liver function tests and liver capsule pain. The patient is often **unaware** of the melanoma lesion, and the primary lesion may in fact **disappear** as the disease progresses.

**EX:** Pt post renal TX has RUQ pain with highly elevated LFTs

## Chest Infection in Transplanted Patients and X-Ray Findings

**Differential Diagnosis of pulmonary syndromes based on radiographic appearance on chest radiograph or computed tomography by rate of disease progression**

| Radiographic abnormality | Rate of disease progression | |
|---|---|---|
| | Acute | Subacute or chronic |
| **Consolidation** | **Any organism** | ▪ Nocardia species<br>▪ Actinomyces species<br>▪ Mycobacteria<br>▪ Fungi<br>▪ Bronchiolitis obliterans syndrome |
| **Bronchopneumonia** | ▪ Community-acquired viruses<br>▪ Atypical bacteria (Mycoplasma, Chlamydophila) | ▪ Mycobacteria<br>▪ Bronchiolitis obliterans syndrome |
| **Diffuse interstitial infiltrates** | ▪ Community-acquired viruses<br>▪ **CMV. EBV. HSV**<br>▪ *Pneumocystis. jirovecii*<br>▪ pulmonary edema, pulmonary haemorrhage<br>▪ Acute respiratory distress syndrome | ▪ Mycobacteria<br>▪ Drug toxicity, radiation toxicity<br>▪ Metastatic cancer<br>▪ Pulmonary alveolar proteinosis |
| **Nodular infiltrates** | ▪ **CMV**<br>▪ Bacteria, septic emboli<br>▪ *P. jirovecii* | ▪ Nocardia species<br>▪ Actinomyces species<br>▪ Mycobacteria<br>▪ Fungi<br>▪ Kaposi sarcoma, Castleman disease<br>▪ Lung cancer |
| **Adenopathy** | ▪ Mycobacterium tuberculosis<br>▪ Cryptococcus neoformans | ▪ Mycobacterium tuberculosis<br>▪ **PTLD**<br>▪ Kaposi sarcoma, Castleman disease<br>▪ Lung cancer |
| **Pleural effusion** | ▪ Bacteria<br>▪ Tuberculosis<br>▪ Postoperative<br>▪ Heart, Kidney, or liver failure | ▪ Non-Hodgkin's lymphoma<br>▪ Primary effusion lymphoma |

***CMV*** cytomegalovirus, ***EBV*** Epstein-Barr Virus, ***HSV*** Herpes Simplex Virus, ***PTLD*** posttransplant lymphoproliferative disorder.

## Peritoneal dialysis

Peritoneal dialysis (PD) is a form of renal replacement therapy. It is sometimes used as a stop-gap to haemodialysis or for younger patients who do not want to have to visit hospital three times a week.

The majority of patients do Continuous Ambulatory Peritoneal Dialysis (CAPD), which involves four 2-litre exchanges/day.

**Complications:** Mechanical: like catheter migration, omental wrap, out-flow failure, in-flow pain **and** non-mechanical: especially peritonitis.

## PD peritonitis

- PD peritonitis is an important complication of peritoneal dialysis.
- A **high suspicion for the diagnosis** is required and **empirical treatment** is often started.
- **PD fluid WCC of greater than 100/mm3** is **diagnostic** of PD peritonitis and should be selected.
- A PD fluid **neutrophil** percentage of **greater than 50%.**
- Raised serum CRP may be associated but is not necessarily diagnostic.
- **10 to 30%** of cases are **culture negative**.
- At **20-25%** overall, **coagulase negative Staphylococcus (CoNS)** is the **most** commonly **cultured** organism, it is a skin commensal that opportunistically causes infection through the catheter site.
- With improved hygiene and technique, rates of staphylococcal infection are falling.
- Intra-abdominal pathology (such as a ruptured viscous) should be considered if more than one organism is grown, especially if Gram negative or anaerobic.
- Repeated treatment increases the risk of resistant organisms. This may require loss of catheter and switch to hemodialysis.
- Contraindication of PD if patient has colostomy or abdominal surgery with possible adhesions.

**Treatment:**

- **Intraperitoneal (IP) antibiotics** is more effective than IV.
- **IP Vancomycin** is necessary in moderate illness.
- **Oral ciprofloxacin** is added to further broaden coverage.
- **IV Vancomycin** would be appropriate for more severe illness.

DP catheter-related peritonitis >>TTT: **IP Vancomycin + Oral ciprofloxacin**

Persistent or relapsing peritonitis, erosion or protrusion of the cuff around the dialysis catheter may unfortunately necessitate **removal**.

Case series report between **11 to 33%** of patients with **CAPD** peritonitis having **pneumoperitoneum** (**AXR**: air under diaphragm), the majority of which can be managed **conservatively** >>> **Intraperitoneal** (**IP**) **Vancomycin** and **Gentamycin** via the dialysis catheter.

## Arteriovenous fistulas

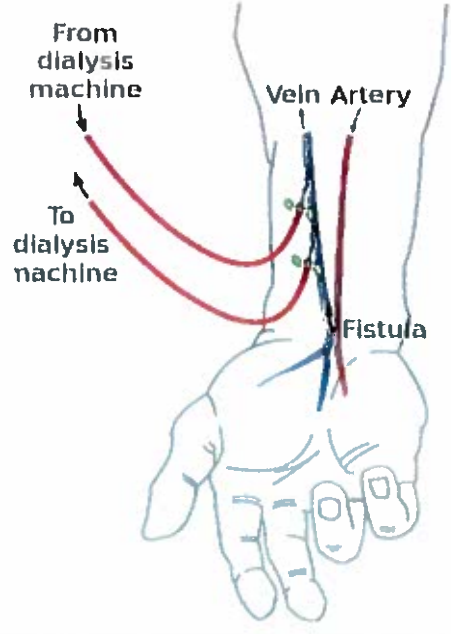
Arteriovenous fistulas are direct connections between arteries and veins. They may occur pathologically but are generally formed surgically to allow access for hemodialysis.

They are now regarded as the **preferred method of access for hemodialysis** due to the lower rates of complications.

**The time taken for an arteriovenous fistula to develop is 6 to 8 weeks.**

### Potential complications include:

- infection
- thrombosis
  - may be detected by the absence of a bruit
- stenosis
  - may present with acute limb pain
- steal syndrome



# Nephrotic syndrome

**Nephrotic syndrome is a cluster of clinical findings associated with some renal diseases, it is combination of:**

- Proteinuria **(> 3.5 g/24hr)**.
- Hypoalbuminemia. (< 30g/L) and
- Oedema.
- hypercholesterolemia.

## Hypercoagulable state is the fifth optional feature.

- Loss of antithrombin-III, proteins C and S in urine and an associated rise in fibrinogen levels predispose to thrombosis together with platelet dysfunction.
- Loss of thyroxin-binding globulin lowers the total, but not free, thyroxine levels.
- 24 hours urine protein is needed for initial diagnosis , follow up later on can be by urine dipsticks and urine albumin /creatinin ratio.
- Remember to exclude other causes of anasarca before exclusively attributing oedema to kidney disease.

## Causes of nephrotic syndrome:

### 1) Primary glomerulonephritis(idiopathic) accounts for around 80% of cases:

- **Minimal** change glomerulonephritis (causes 80% in children, 30% in adults).
- **Membranous** glomerulonephritis.
- **FSGS** Focal segmental glomerulosclerosis.
- **Membranoproliferative** glomerulonephritis.

**In adults IgA nephropathy, fibrillary and immunotactoid GN can present also with nephrotic syndrome**

### 2) Systemic disease (about 20%):

- DM.
- SLE.
- Amyloidosis.
- Post infectious glomerulonephritis.
- Henoch-Schoenlein purpura.
- Infections(hepatitis B,C and HIV).
- Hematological malignancies like Hodgkin's disease.

### 3) Drugs:

- Gold (Sodium aurothiomalate) (auranofin).
- Penicillamine.

Nephrotic syndrome > drug causes >> Gold (Sodium aurothiomalate) (auranofin) & **Penicillamine.**
Removal of Gold therapy in RA often leads to a significant improvement in the degree of proteinuria.

**Nephrotic** syndrome - **malignancies** cause **membranous** glomerulonephritis

- Patients with underlying malignancies such as lung, colon and gastric cancer may develop nephrotic syndrome as a **Paraneoplastic complication.** There appears to be an association with **HLA-DR3.**
- **Lymphomas** tend to be associated with **minimal change** disease.

**Complications** of nephrotic syndrome:

- ↑ Risk of **infection** (especially **pneumococcal** infections) due to urinary IgG loss, reduced complement function and decreased splanchnic blood flow.
- ↑ Risk of **thromboembolism (DVT/PE)** due to:
  - **Loss** of **anti-thrombin III (AT III)** and plasminogen in urine.
  - With **increased** fibrinogen and increased factor VIIIc.
  - Intravascular volume depletion (exacerbated by diuretics).
- **Hyperlipidaemia.**
- **Hypocalcaemia** due to loss of vitamin D and binding protein in urine.
- **ARF** due to **renal vein thrombosis** which occurs in **10-20%** of patients with nephrotic syndrome (loin pain + haematuria): initial investigation is US: swollen oedematous kidney more than other side,

**Treatment: long term anticoagulation.**

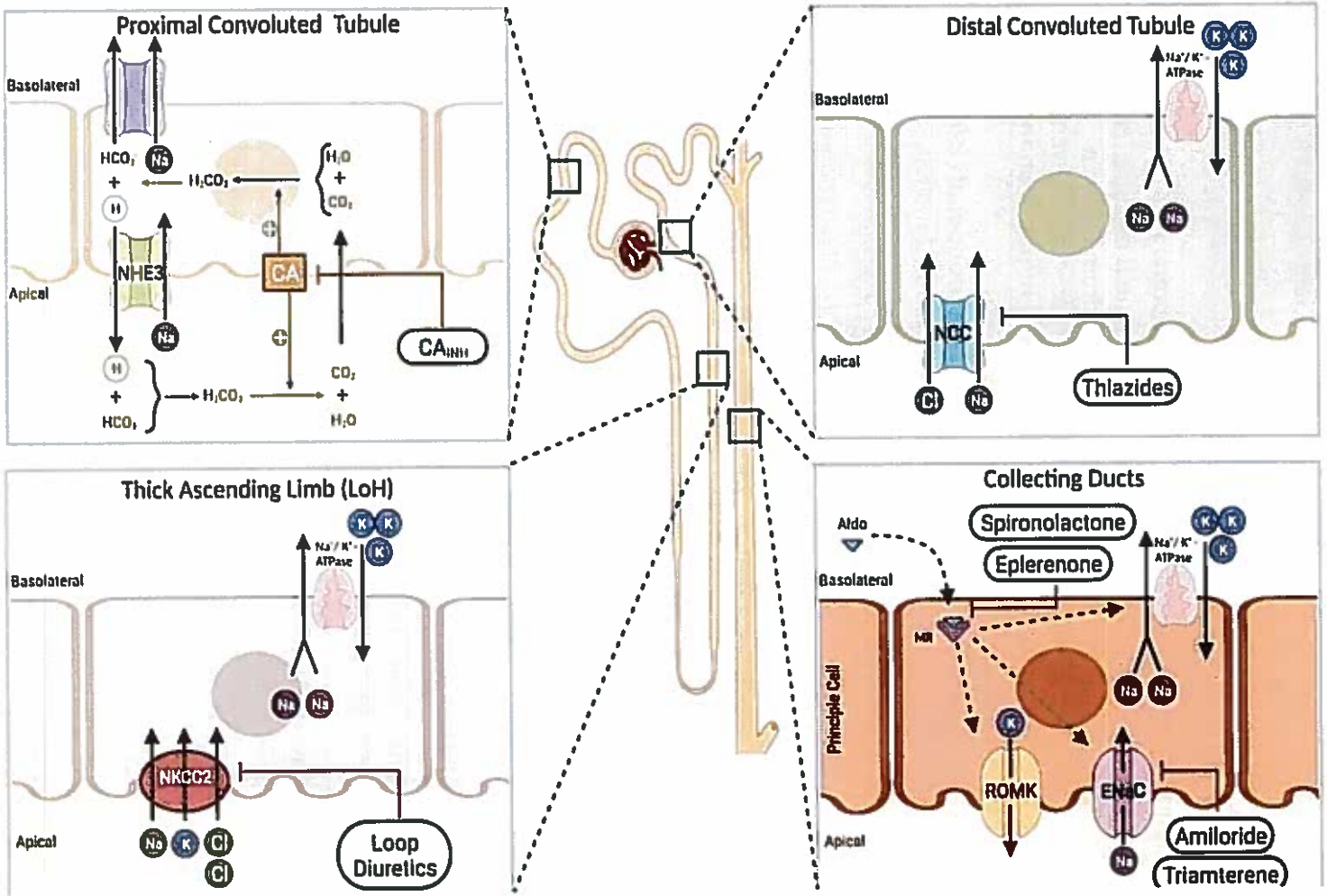
Any patient with nephrotic syndrome, then develop **flank pain, haematuria, worsening creatinine, proteinuria** and **LL oedema >> Renal vein thrombosis**
**EX:** female pt. with **SLE** (**membranous** GN) with **nephrotic range proteinuria** and generalized oedema, develop bilateral **loin pain, tenderness, fever** and **haematuria >>> Renal vein thrombosis.**
**Diagnosis:** Duplex US renal veins, CT or MRV.
**Treatment:** mobilisation, avoid volume depletion, anticoagulation.

**EX: Old** female 77 years old with **DVT** and **nephrotic** syndrome (**membranous**) >>> the most **direct link** between her DVT and membranous nephropathy is: **1) Antithrombin deficiency, 2) underlying malignancy.**

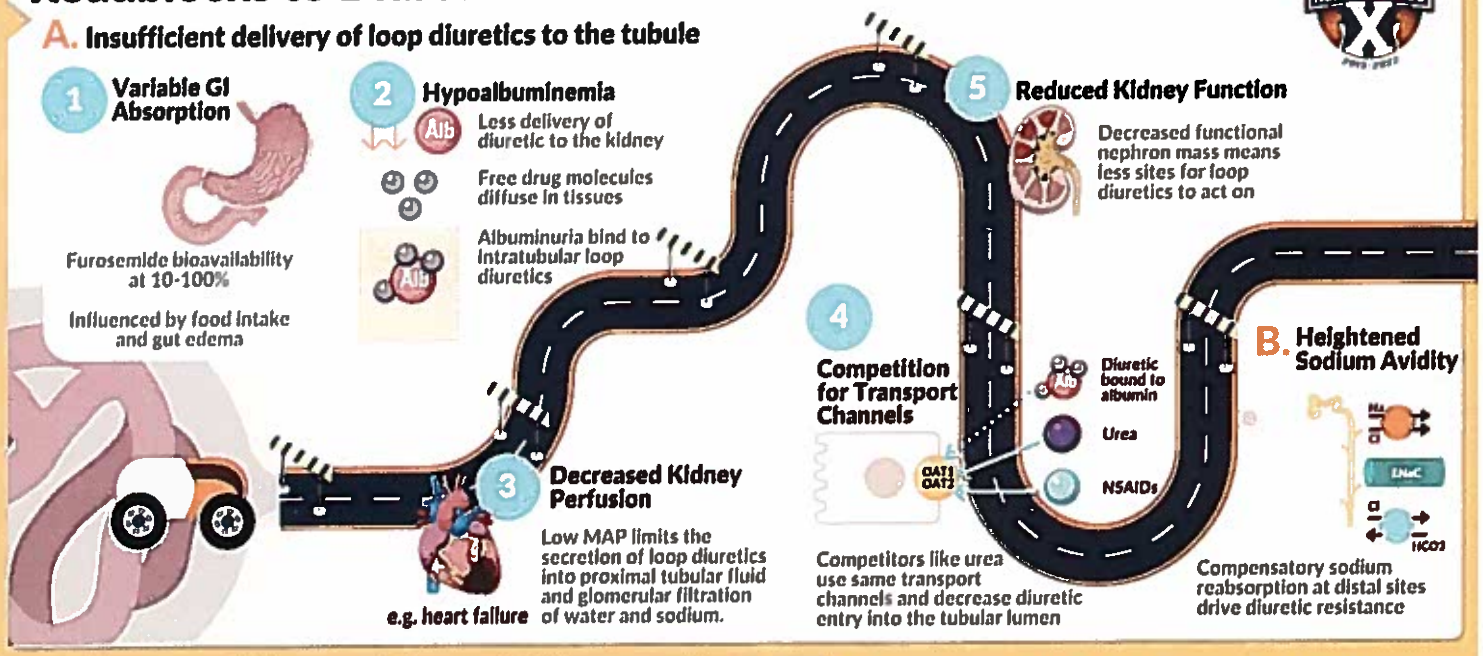
**Important points in management of nephrotic syndrome:**

- Restrict dietary sodium.
- Frusemide help to reduce oedema but must not over prescribed to avoid dehydration.

# Diuretics


Proximal Convoluted Tubule
Basolateral
Apical
NHE3
CA
CA$_{INH}$
Distal Convoluted Tubule
Basolateral
Apical
NCC
Thiazides
Thick Ascending Limb (LoH)
Basolateral
Apical
NKCC2
Loop Diuretics
Collecting Ducts
Aldo
Spironolactone
Eplerenone
Basolateral
Principle Cell
ROMK
ENaC
Amiloride
Triamterene
Apical

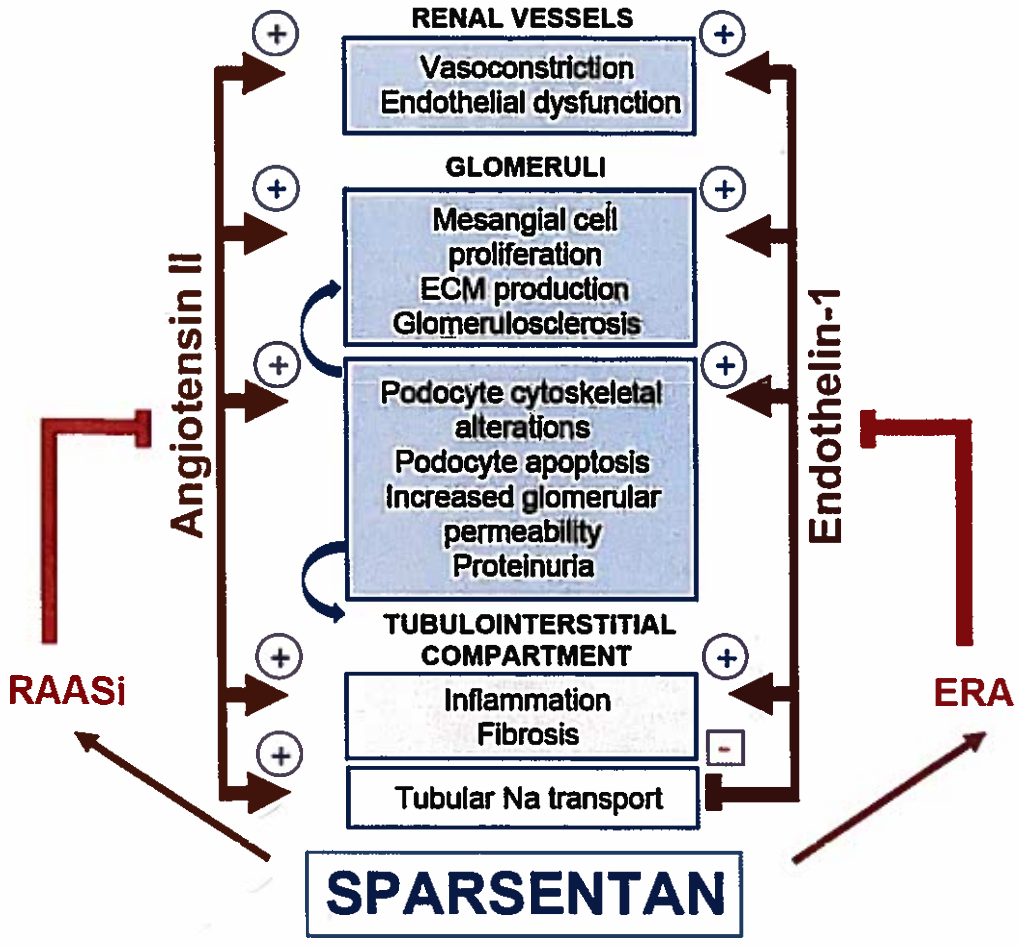
# Roadblocks to Diuresis: Mechanisms of Diuretic Resistance


A. Insufficient delivery of loop diuretics to the tubule
1 Variable GI Absorption
Furosemide bioavailability at 10-100%
Influenced by food intake and gut edema
2 Hypoalbuminemia
Alb
Less delivery of diuretic to the kidney
Free drug molecules diffuse in tissues
Albuminuria bind to intratubular loop diuretics
3 Decreased Kidney Perfusion
Low MAP limits the secretion of loop diuretics into proximal tubular fluid and glomerular filtration of water and sodium.
e.g. heart failure
4 Competition for Transport Channels
OAT1
OAT2
Diuretic bound to albumin
Urea
NSAIDs
Competitors like urea use same transport channels and decrease diuretic entry into the tubular lumen
5 Reduced Kidney Function
Decreased functional nephron mass means less sites for loop diuretics to act on
B. Heightened Sodium Avidity
NHE
ENaC
HCO3
Compensatory sodium reabsorption at distal sites drive diuretic resistance

**Conclusion:** Diuretic resistance is the failure to decongest despite adequate and escalating doses of diuretics. Major mechanisms leading to diuretic resistance include insufficient delivery of diuretic to the proximal tubule (affected by absorption, hypoalbuminemia, renal function and perfusion and competing molecules) and compensatory distal sodium reabsorption.

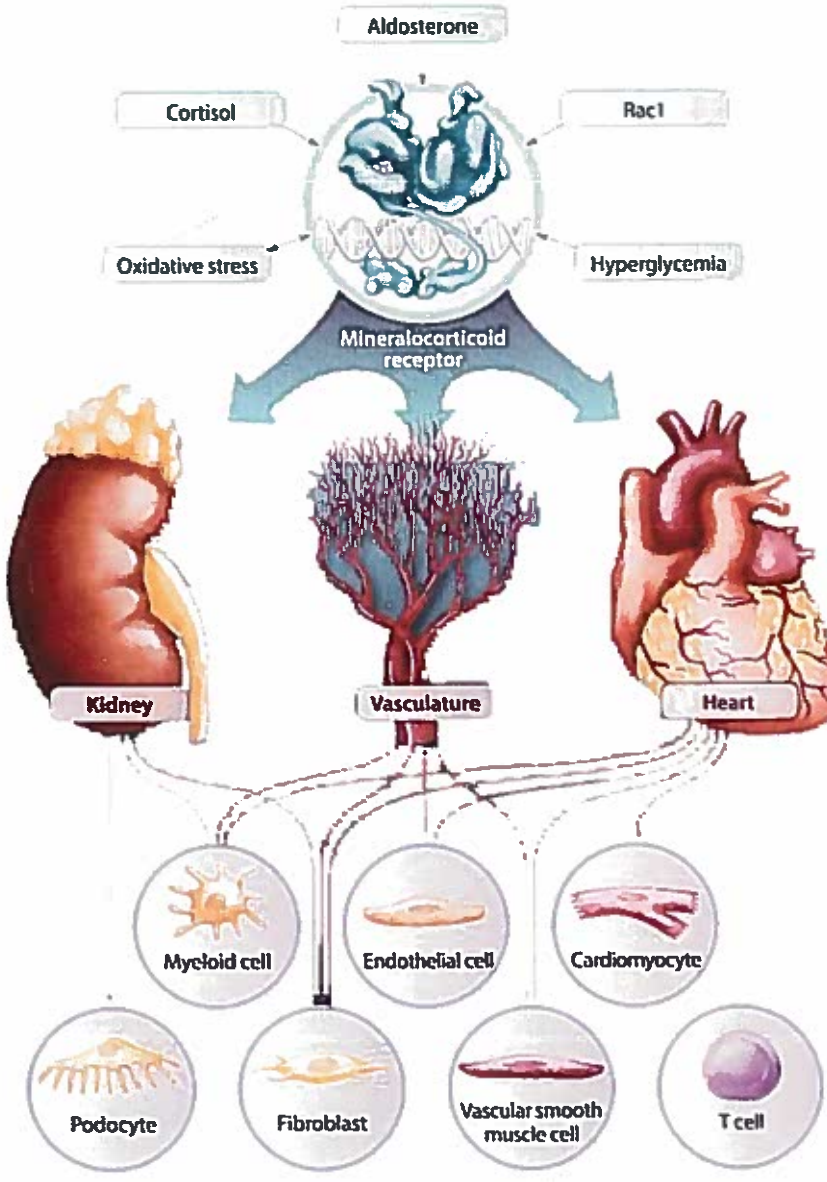
**Reference:** Gupta et al. *Diuretic Resistance in Heart Failure.* 2019

- In patients with morbidly obese, have heart failure. proteinuria more than 10 grams/day and history of DVT **Should Receive Therapeutic Anticoagulation**
- High dose prednisolone is useful in minimal change disease.
- High protein diet is not beneficial, and patient are kept on normal protein diet.
- Albumin IV produces only a transient rise in serum levels, and only given if s. albumin below 2 mg/dl or marked oedema
- Prophylactic antibiotics are not recommended, however vaccinations e.g., pneumococcal vaccine can be used.
- HMG-COA reductase for hypercholesterolemia is prescribed in patients with chronic glomerular diseases and not those who have hyperlipidaemia rapidly corrected by proper treatment like minimal change disease.
- Use on of RAAS inhibitors to reduce proteinuria, and don't use 2 drugs at the same time from this group of treatment.
- If RAAS inhibitors are contraindicated duo to their side effects such as hyperkalaemia, dry cough or significant rise of serum creatinine or in advanced kidney disease with GFR below 30%. We can use non-dihydropyridine calcium channel blockers with or without endothelin receptors antagonists, or combination of hydralazine and nitrates.




Schematic presentation of major similarities and differences in physiological and pathophysiological actions of angiotensin II and endothelin-1 in the kidney

**cascades of injury, inflammation, and fibrosis that are initiated sustained by MR activation**




Complementary interplay of cascades of injury, inflammation, and fibrosis that are initiated and sustained by MR activation. The MR is activated by several ligands (eg, aldosterone and cortisol) and by nonligand activation. MR expression occurs in numerous tissues, including nonepithelial tissues. Multipronged and complementary systemic and local molecular and signaling mechanisms act on the various cell types to promote cardiovascular and kidney injury. Abbreviations: MR, mineralocorticoid receptor; Rac1, Rac family small guanosine triphosphatase 1

## Nephritic syndrome (Glomerulonephritides) consists of:

- Oliguria.
- Acute renal failure.
- Haematuria.
- Hypertension.
- Proteinuria.
- Oedema.

**Outcome and treatment of nephritic syndrome depends on nature and histopathology of each individual disease.**

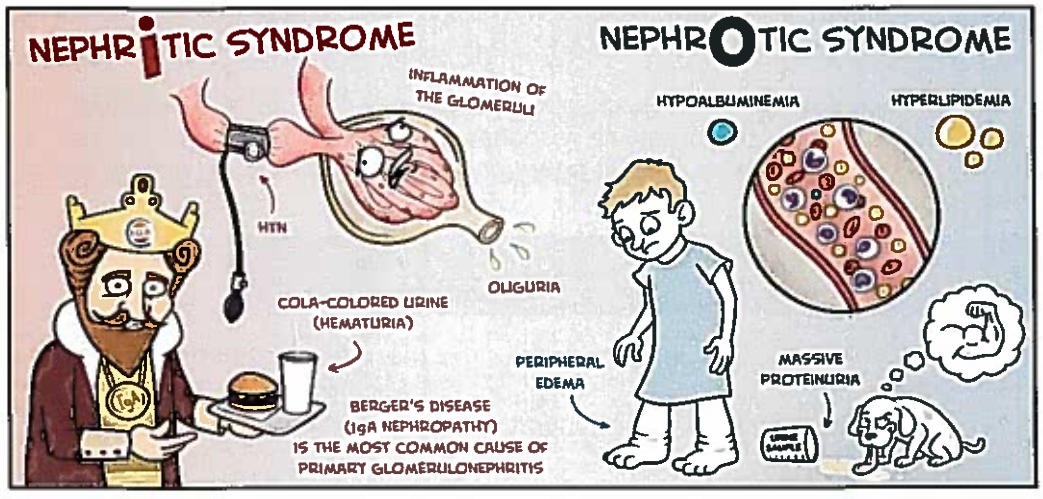



Diagram showing the glomerulonephritides and how they typically present

| Nephritic syndrome (haematuria, hypertension) | | Nephrotic syndrome (proteinuria, oedema) |
|---|---|---|
| | | Minimal change disease |
| Rapidly progressive GN | Diffuse proliferative GN | Membranous GN |
| IgA nephropathy | Membranoproliferative GN | Focal segmental glomerulosclerosis |
| Alport syndrome | Post-streptococcal GN | Amyloidosis |
| | | Diabetic nephropathy |

| Criteria | Definition |
|---|---|
| Complete response* | • Reduction in proteinuria <0.5 g/g (50 mg/mmol) measured as the PCR from a 24-h urine collection<br>• Stabilization or improvement in kidney function (±10%–15% of baseline)<br>• Within 6–12 mo of starting therapy, but could take more than 12 mo |
| Partial response | • Reduction in proteinuria by at least 50% and to <3 g/g (300 mg/mmol) measured as the PCR from a 24-h urine collection<br>• Stabilization or improvement in kidney function (±10%–15% of baseline)<br>• Within 6–12 mo of starting therapy |
| No kidney response | • Failure to achieve a partial or complete response within 6–12 mo of starting therapy |

Commonly used definitions of response to therapy in GLOMERULONEPHRITIS. *For children <18 years old, complete response is defined as proteinuria <0.5 g/1.73 $m^2$/d or <300 mg/$m^2$/d based on a 24-hour urine specimen. LN, lupus nephritis; PCR, protein-creatinine ratio.

# Glomerular diseases

## KDIGO 2021 clinical practice guideline for the management of glomerular diseases

Knowing a few **key facts** is the best way to approach the difficult subject of glomerulonephritis:

- Minimal change disease:
- Membranous glomerulonephritis:
- IgA nephropathy (Berger's disease, mesangioproliferative GN)
- Diffuse proliferative glomerulonephritis
- Focal segmental glomerulosclerosis (FSGS):
- Rapidly progressive glomerulonephritis (crescentic GN)
- Mesangiocapillary glomerulonephritis (membranoproliferative):

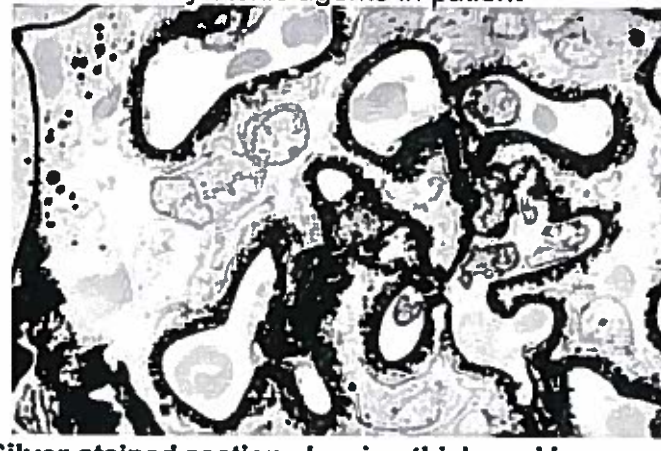
### 1) Minimal change disease: (See later)

- Typically, a child with nephrotic syndrome (accounts for 80%)
- Causes: primary idiopathic
- Secondary: Hodgkin's lymphoma, NSAIDs, hepatitis B and C.
- Presents with mild to sever oedema others are:abdominal pain ,diarrhea ,poor appetite and decreased urine output.
- Treated by steroids 60mg/m2 for 6 weeks then 40 mg/m2 every other day for another 6 weeks in children.

- In adults :1mg/kg/day maximum 80 mg/ day for 2 months which may extend to another 2 month if late remitters, then reduce the dose gradually over longer time to ensure good remission and avoid adrenal insufficiency

## 2) Membranous glomerulonephritis: (See later)

- Presentation: proteinuria / nephrotic syndrome / chronic kidney disease
- Cause: infections (hepatitis B, C and HIV, rheumatic diseases and their drugs, malignancy (solid tumors)
- 1/3 resolve, 1/3 respond to cytotoxic medications , 1/3 develop chronic kidney disease.
- Factors associated with poor prognosis:
  - Advanced age.
  - Male sex.
  - Elevated blood pressure.
  - CKD
  - Severity of initial proteinuria.
  - Persistant proteinuria more than 4 grams/day,in addition to tubular atrophy, interstitial fibrosis, glomerulosclerosis, and high level of B2 macroglobulin in urine, all are strongest predictor of progressive kidney disease in membranous nephropathy.
- Treatment by pontichelli protocol which is 6 months of alternating steroids with cytotoxic agents in patient



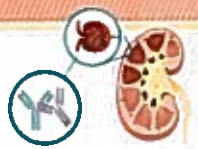
- **Silver-stained section showing thickened basement membrane, subepithelial spikes**

## 3) IgA nephropathy (Berger's disease), mesangioproliferative GN: (See later)

- Typically, young adult with hematuria following an URTI.

# The "Four Hit" IgA Nephropathy (IgAN) Pathogenesis Theory

NephU
Improving Awareness & Patient Outcomes



## Pathogenesis of IgA Nephropathy (IgAN)

Normally, immunoglobulin A (IgA) is produced on the body's mucosal surfaces as part of the innate immune response. However, in patients with IgAN a **galactose-deficient IgA (Gd-IgA1)** is produced leading to an autoimmune response, deposition of Gd-IgA1 containing immune complexes in the kidney tissue, and ultimately kidney injury. The current model of pathogenicity in IgAN involves four hits that drive disease development and progression.[1]

### Hit #1

**Production of aberrant, galactose-deficient IgA1 (Gd-IgA1), by plasma cells.**[1]

### Hit #2

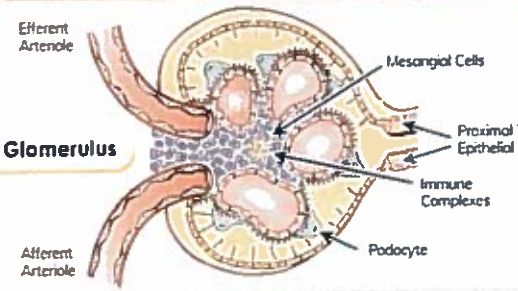
Synthesis of **autoantibodies** directed against the aberrant, Gd-IgA1.[1]

### Hit #3

Binding of autoantibodies to the Gd-IgA1 generates **pathogenic immune complexes**, which circulate in the bloodstream.[1]

### Hit #4

Circulating immune complexes deposit at the points of filtration (mesangial cells, located between glomerular basement membrane and fenestrated endothelium of the kidney). **Deposition of immune complexes result in local immune activation, inflammation, and glomerular injury.**




## Outcome Of The Four Hit Pathogenic Process:

- Injury to the podocytes and proximal tubular epithelial cells
- Worsening kidney function progressing to chronic kidney disease.
- Which left unaddressed, can lead to kidney failure and the need for renal replacement therapy, such as transplant or dialysis.[1,4]

## For More Information on IgAN:

- IgA Nephropathy Foundation: **IgAN.org**
- National Kidney Foundation: **Kidney.org**
- KDIGO 2021 Clinical Practice Guideline For the Management Of Glomerular Diseases: **KDIGO.org/guidelines/gd**

## IgAN Clinical Trials

As we learn more about the pathophysiology of IgAN, there are more clinical trials targeting various "hits" within the overall disease process.

Patient participation in clinical trials is crucial for evaluating novel therapies for IgAN.[2] A full listing of the 100+ IgAN clinical trials can be found at[3] **clinicaltrials.gov.**

## Potential New Diagnostic & Prognostic Markers

**In Blood:**

Serum levels of galactose-deficient IgA1 (Gd-IgA1) protein may serve as a diagnostic test, as they may be significantly elevated long before IgAN diagnosis.[1]

**In Urine:**

Noninvasive tests for IgAN through urinary proteomics may detect a subset of mesangial immune complexes, or Gd-IgA1 within immune complexes.[1]

**Genetic:**

A genome-wide association study (GWAS) of "sporadic IgAN identified five novel genetic variants with relatively strong protective effects against IgAN."[1]

## 4) Diffuse proliferative glomerulonephritis:

- Classical **post-streptococcal glomerulonephritis** in child
- Presents as nephritic syndrome / acute kidney injury
- Most common form of renal disease in **SLE (class 4)**

**Diffuse proliferative glomerulonephritis**, causes:
- Post-streptococcal
- SLE (class 4)

## 5) Focal segmental glomerulosclerosis (FSGS):

- May be idiopathic or secondary to **HIV**, **HBV**, **IV drug abuser**, and **heroin.**
- Presentation: **proteinuria** / **nephrotic** syndrome / CKD.
- It leads to chronic renal failure in 50% of cases.
- It accounts for approximately 20% of cases of nephrotic syndrome in children and 40% in adults.
- It is one of the most common primary glomerular disorders causing ESRD.
- **A significant number of patients with FSGS go on to ESRD.**
- Unfortunately, **FSGS recurs in 40% of renal transplants** .
- Early in the disease course, **glomerulosclerosis** involves a **minority of glomeruli (focal)** and only a portion of the glomerular globe **(segmental).** As the disease progresses more widespread glomerulosclerosis develops.
- Causes:
  - **Idiopathic** (in **80%**)
  - Secondary to other renal pathology e.g.
    - Viral (**HIV**, HBV, parvovirus B19, CMV, EBV),
    - Drug-induced (**Heroin**, IFN, lithium, pamidronate, anabolic steroids, calcineurin inhibitors).
    - Adaptive (unilateral renal agenesis, HTN, **sickle cell anemia**, Vaso-occlusion).
    - Reflux nephropathy.
      - Genetic: many genes were found to cause FSGS SOME ARE INHERETED AS A.D OTHERS ARE A.R.

Approximately **50% of subjects with FSGS** do **not respond to steroid therapy** but **ACEIs** are a recognized strategy to slow the progression of renal disease.
If FSGS is glucocorticoid resistant, therapy is with a **calcineurin inhibitor.**
In HIV associated FSGS, HAART is associated with a reduction of proteinuria.

## 6) Rapidly progressive glomerulonephritis (crescentic glomerulonephritis):

- Rapid onset, often presenting as acute kidney injury
- Causes include **Goodpasture's**, **ANCA positive vasculitis**

**Rapidly progressive glomerulonephritis, causes:**

- Goodpasture's
- ANCA positive vasculitis such as Wegener's granulomatosis, microscopic polyangiitis

## 7) Mesangiocapillary glomerulonephritis (membranoproliferative):

- Type 1: cryoglobulinemia, hepatitis C >>>>> low **C4.**
- Type 2: partial lipodystrophy >>>>> low **C3.**

### Overview:

- Also known as mesangiocapillary glomerulonephritis.
- May present as nephrotic syndrome, hematuria or proteinuria.
- Poor prognosis.

### Type 1:

- Accounts for 90% of cases.
- **Sub-endothelial immune deposits** of electron dense material resulting in a **'tram-track' appearance.**
- Cause: cryoglobulinemia, hepatitis C (with ↓ **C4).**

### Type 2: dense deposit disease' (DDD):

- **Intra-membranous** deposits of electron dense material.
- Causes: **partial lipodystrophy, factor H deficiency.**
- **Reduced** serum complement ( ↓ **C3).**
- **C3b nephritic factor** (an antibody against C3bBb) found in 70%.

### Type 3:

- Causes: hepatitis B and C

### Management:

- Steroids may be effective.

More details
For Specialists and As A Refferance

# Minimal change disease

Minimal change disease nearly always presents as nephrotic syndrome, accounting for 75% of cases in children (peak incidence 2-3 years of age) and 25% in adults.

**Nephrotic** syndrome in **children / young adults - minimal change glomerulonephritis**

**The majority of cases** are idiopathic, but in around 10-20% a cause is found:

- Drugs: NSAIDs, rifampicin
- Hodgkin's lymphoma, thymoma
- Infectious mononucleosis

## Pathophysiology:

- T-cell and cytokine mediated damage to the glomerular basement membrane → **polyanion loss**
- The resultant **reduction** of **electrostatic charge** → increased glomerular permeability to serum albumin.

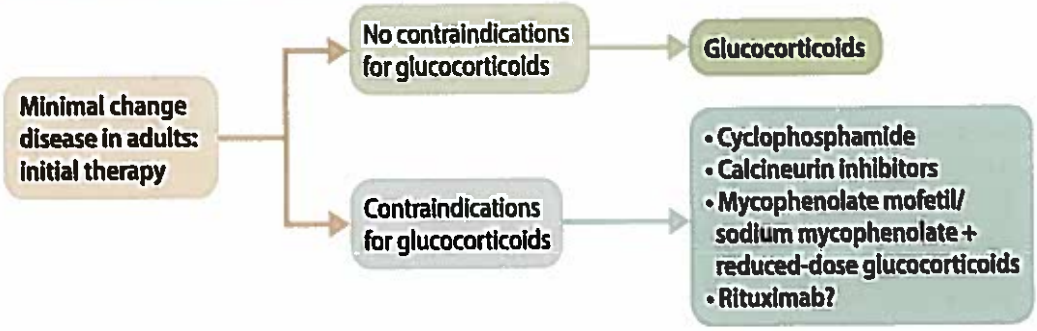
## Features:

- **Nephrotic** syndrome
- Normotension (hypertension is rare)
- Highly selective proteinuria(only albumniurea)
- Hematuria is rare
- Renal biopsy:
  - **Light** microscopy: NORMAL
  - **Electron** microscopy shows **fusion of podocytes** with normal Basement membrane.

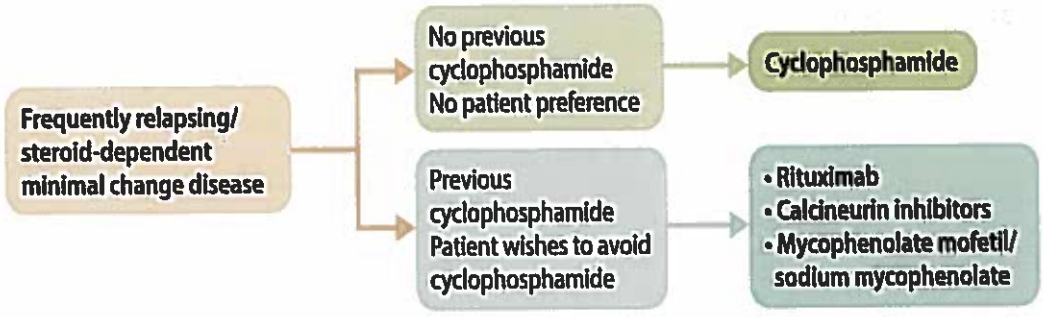
Podocyte's fusion is seen in minimal change GN but may occasionally be a feature of FSGS as well. Minimal change however is far more common.

## Management:

- Majority of cases **(80%)** are **extremely steroid responsive** and achieving remission **within 8 weeks** with **prednisolone 60 mg daily**.
- Cyclophosphamide is the next step for steroid resistant cases.
- **Anticoagulation** with LMWH as **ATIII deficiency** is likely as nephrotic often lose antithrombin in the urine and patient is liable to **DVT/PE** or **renal vein thrombosis**.




Initial treatment of MCD in adults. The optimal glucocorticoid regimen is not well defined; however, suggested doses are outlined in Figure 45 of the full guideline. The choice of medication should be based on physician and patient preference. MCD, minimal change disease.


Frequently relapsing/ steroid-dependent minimal change disease
No previous cyclophosphamide No patient preference
Cyclophosphamide
Previous cyclophosphamide Patient wishes to avoid cyclophosphamide
• Rituximab
• Calcineurin inhibitors
• Mycophenolate mofetil/ sodium mycophenolate

Treatment of frequently relapsing/steroid-dependent MCD in adults. The choice of medication should be based on physician and patient preference. MCD, minimal change disease. KDIGO execut i v e conclusions BH Rovin et al.
Executive summary of KDIGO 2021 glomerular diseases

**Prognosis** is overall **good**, although **relapse is common**. Roughly:

- 1/3 have just one episode
- 1/3 have infrequent relapses
- 1/3 have frequent relapses which stop before adulthood

**N.B:** The optimal glucocorticoid regimen is not well defined; however, The choice of medication should be based on physician and patient preference.

**In children, 30 to 40%** achieve **spontaneous remission** and **90%** achieve **remission following 8 weeks treatment with high dose steroids.**

However, in **adults only around 50%** achieve **remission.**

*Only intermediate-sized proteins such as albumin and transferrin leak through the glomerulus.

# Focal segmental glomerulosclerosis (FSGS) in adults

## Primary FSGS:

Primary FSGS as a clinical–pathologic syndrome in which light microscopy of the kidney biopsy demonstrates FSGS lesions, electron microscopy of the kidney biopsy demonstrates diffuse foot process effacement, and clinically the patients display NS.

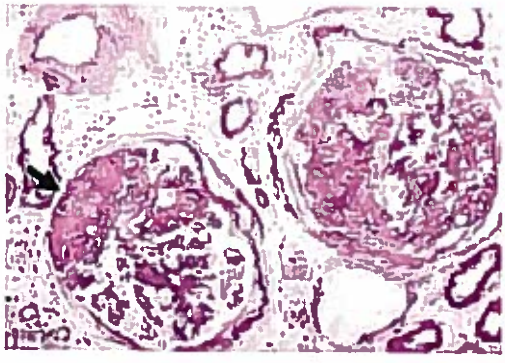
When considering adiagnosis of primary FSGS, there should be no other identifiable causes of FSGS

Focal segmental glomerulosclerosis is noted for having a high recurrence rate in renal transplants.

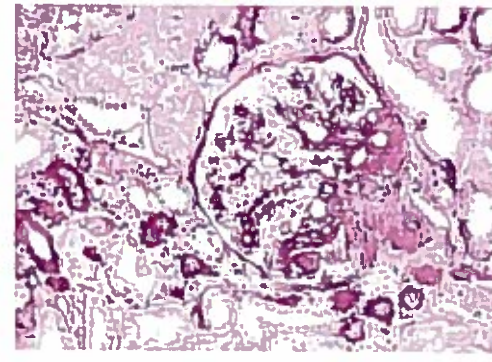
## Investigations

### Renal biopsy

- focal and segmental sclerosis and hyalinosis on light microscopy
- effacement of foot processes on electron microscopy



Sclerosis of the glomerulus is seen next to Bowman's capsule



Sclerosis is seen in the perihilar region of the glomerulus

## Secondary FSGS:

When an FSGS lesion, with or without the presence of diffuse podocyte foot process effacement, is found in the setting of an established pathophysiologic process known to cause FSGS, **we refer to this as secondary FSGS.**

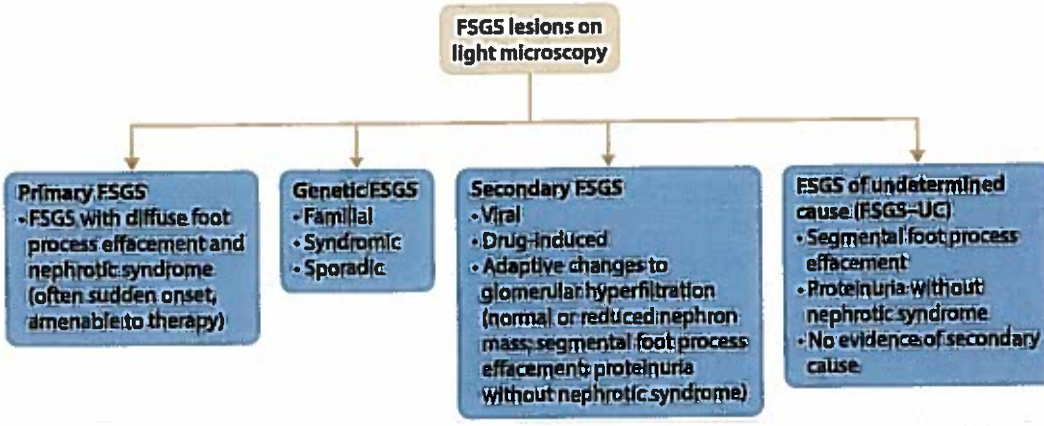
- idiopathic
- secondary to other renal pathology e.g., IgA nephropathy, reflux nephropathy
- HIV
- heroin

- Alport's syndrome
- sickle-cell

## Genetic FSGS:

FSGS lesions may develop in patients who have mutations in podocyte or glomerular basement membrane proteins. The search for a genetic cause is not routine in adults with FSGS.

## Classification of FSGS


FSGS lesions on light microscopy
Primary FSGS
• FSGS with diffuse foot process effacement and nephrotic syndrome (often sudden onset, amenable to therapy)
Genetic FSGS
• Familial
• Syndromic
• Sporadic
Secondary FSGS
• Viral
• Drug-induced
• Adaptive changes to glomerular hyperfiltration (normal or reduced nephron mass; segmental foot process effacement; proteinuria without nephrotic syndrome)
FSGS of undetermined cause (FSGS-UC)
• Segmental foot process effacement
• Proteinuria without nephrotic syndrome
• No evidence of secondary cause

**Proposed classification of FSGS.** FSGS, focal segmental glomerulosclerosis.

## Treatment:

**1.**

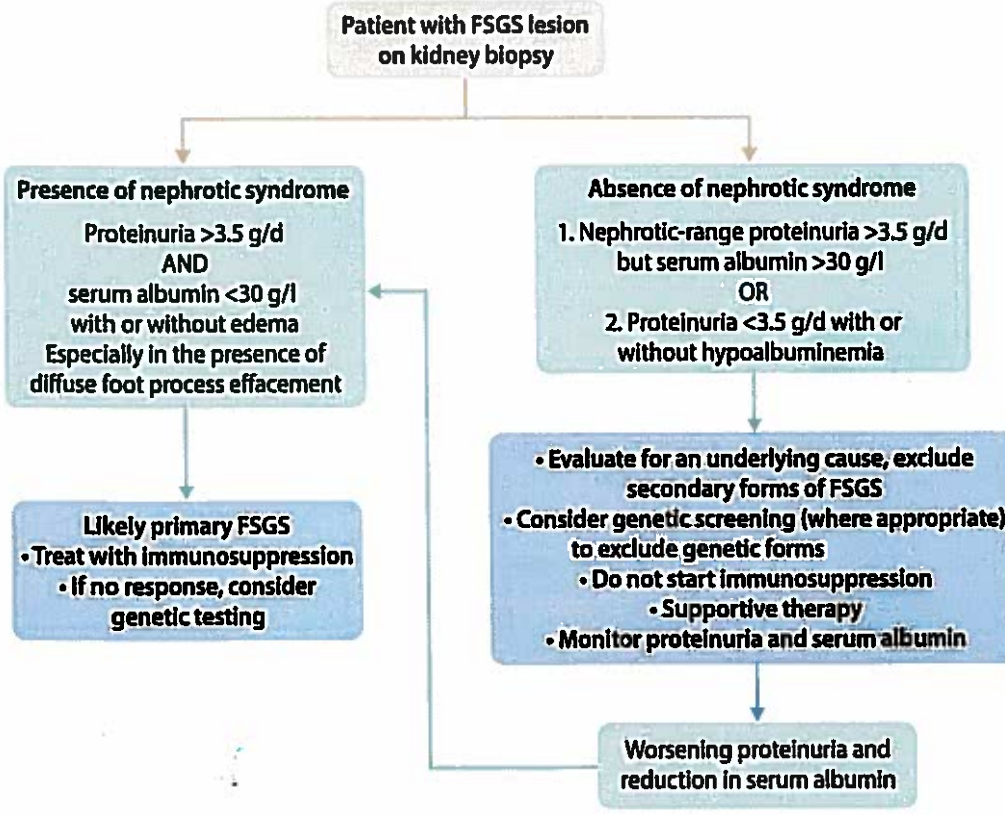
a) Adults with primary FSGS who respond to glucocorticoid treatment should receive glucocorticoid.
b) High dose oral glucocorticoids be used as the first line immunosuppressive treatment for primary FSGS. Initial high-dose glucocorticoids should be continued until complete remission is achieved, or as tolerated by patients up to a maximum of 16 weeks, whichever is earlier. Adults with primary FSGS who respond to glucocorticoid treatment should receive glucocorticoids for 6 months or more.
c) In adults with relative contraindications or intolerance to glucocorticoids, alternative immunosuppression with CNIs should be considered as the initial therapy in patients with primary FSGS.

**Adults with steroid-resistant primary FSGS who respond to CNI treatment should receive CNIs for a minimum of 12 months to minimize the risk of relapses**

**2.**

Immunosuppression should not be used in adults with FSGS of undetermined cause (FSGS-UC), or in those with secondary FSGS.

## SUMMARY OF FSGS TREATMENT




Evaluation of a patient with FSGS lesion on the kidney biopsy and no evidence of other glomerular pathology.

| Treatment | Dose and duration |
|---|---|
| Glucocorticoids | **Starting dose:**<br>• High-dose glucocorticoid therapy with prednisone at daily single dose of 1 mg/kg (maximum 80 mg) or alternate-day dose of 2 mg/kg (maximum 120 mg) |
| | **High-dose glucocorticoid treatment duration:**<br>• Continue high-dose glucocorticoid therapy for at least 4 weeks and until complete remission is achieved, or a maximum of 16 weeks, whichever is earlier<br>• Patients who are likely to remit will show some degree of proteinuria reduction before 16 weeks of high-dose treatment<br>• It may not be necessary to persist with high-dose glucocorticoid therapy until 16 weeks if the proteinuria is persistent and unremitting, especially in patients who are experiencing side effects |
| | **Glucocorticoid tapering:**<br>• If complete remission is achieved rapidly, continue high-dose glucocorticoid treatment for 2 weeks or after the disappearance of proteinuria, whichever is longer. Reduce prednisone by 5 mg every 1–2 weeks to complete a total duration of 6 months<br>• If partial remission is achieved within 8 to 12 weeks of high-dose glucocorticoid treatment, continue until 16 weeks to ascertain whether further reduction of proteinuria and complete remission may occur. Thereafter, reduce the dose of prednisone by 5 mg every 1–2 weeks to complete a total duration of 6 months<br>• If the patient proves to be steroid-resistant or develops significant toxicities, glucocorticoids should be rapidly tapered as tolerated and treatment with alternative immunosuppression like a CNI should be considered |
| Calcineurin inhibitors* | **Starting dose:**<br>• Cyclosporine 3–5 mg/kg/d in 2 divided doses OR tacrolimus 0.05–0.1 mg/kg/d in 2 divided doses<br>• Target trough levels could be measured to minimize nephrotoxicity<br>• Cyclosporine target trough level: 100–175 ng/ml (83–146 nmol/l)<br>• Tacrolimus target trough level: 5–10 ng/ml (6–12 nmol/l) |
| | **Treatment duration for determining CNI efficacy:**<br>• Cyclosporine or tacrolimus should be continued at doses achieving target trough level for at least 4–6 months, before considering the patient to be resistant to CNI treatment |
| | **Total CNI treatment duration:**<br>• In patients with partial or complete remissions, cyclosporine or tacrolimus should be continued at doses achieving target trough level for at least 12 months to minimize relapses<br>• The dose of cyclosporine or tacrolimus can be slowly tapered over a course of 6–12 months as tolerated |

Treatment protocols for FSGS. *The target ranges for CNIs have been based on the transplant literature. The KDIGO Work Group acknowledge that targets for glomerular diseases are not known. Most clinicians check these levels to verify adherence and avoid CNI toxicity. At present, the most reasonable dosing of a CNI may be to titrate in the individual patient to obtain the desired effect on proteinuria, balancing dose escalation against serum creatinine and reducing the dose if serum creatinine increases but does not plateau or increases over 30% of baseline. If the serum creatinine level does not fall after dose reduction, the CNI should be discontinued. CNI, calcineurin inhibitor; FSGS, focal segmental glomerulosclerosis.

# Membranous glomerulonephritis

- Membranous glomerulonephritis is the **commonest** type of GN in **adults**.
- It usually presents with **nephrotic** syndrome or proteinuria.
- It accounts **20-30%** of **adult's nephrotic** syndromes.
- It is the **third** most common cause of **ESRF** (after FSGS).
- **Elderly** in the over **40 age** group patients, **Male twice** than female **(2:1).**

## Renal biopsy demonstrates:

- **Light** microscopy: **The capillary walls are thickened. Sub epithelial deposits** are seen.
- **Electron** microscopy: **the glomerular basement membrane is thickened** with **sub epithelial electron dense deposits (monotonous granular deposits of IgG and C3).** This creates a **'spike and dome'** appearance.
- Practice Point: A kidney biopsy is not required to confirm the diagnosis of membranous nephropathy (MN) in patients with nephrotic syndrome and a positive anti-PLA2R antibody test.
- Practice Point: Patients with MN should be evaluated for associated conditions, regardless of whether anti-PLA2R antibodies and/or anti-THSD7A antibodies are present or absent.
  - Chest x-ray for sarcoidosis.
  - Tumour markers for malignancy according to age and sex.
  - History of drug use (NSAIDs, gold and penicillamine)
  - ANA.
  - HEP.B&C with HIV (and treponema if required).
  - Ultrasound of the kidneys.
  - Full history(systemic and thyroid disease) and physical examination.

## Causes:

- **Idiopathic**: in **60 %** of cases.
- **Infections: HBV, HCV, HIV, Malaria,** Syphilis, Leprosy, schistosomiasis.
- **Autoimmune** diseases: RA, **SLE (class V 5 disease), Thyroid.**
- **Drugs**: **Gold**, penicillamine, NSAIDs, Captopril, heavy metals e.g. mercury, cadmium.

- **Malignancy: lung cancer, leukaemia, lymphoma**, melanoma, breast, stomach, colon, prostate (in fact **only 5-10%** of cases are associated with an underlying cancer).
- **Sickle** cell disease.
- **DM**

**Prognosis** - rule of thirds:

- 1/3: spontaneous remission
- 1/3: remain with proteinuria
- 1/3: develop ESRF within 10 years of diagnosis : In patients with MN,
- use clinical and laboratory criteria to assess the risk of progressive loss of kidney function.
- Patients with membranous nephropathy are classified into:

**Low risk:**

Normal GFR and proteinuria below the nephrotic range and normal serum albumin. and /or decrease of proteinuria more than 50% after 6 months of conservative treatment with ACEi OR ARBs.

**Moderate risk:**

Normal GFR and proteinuria (> 3.5 grams/dl) but less than 8g/dl and no decrease of proteinuria more than 50% after 6 months of conservative treatment with ACEi OR ARBs AND not fulfilling high risk criteria.

**High risk:**

eGFR < 60 ml/min, and/or proteinuria >8 g per day for more than 6 months.

**OR**

Normal GFR and proteinuria (> 3.5 grams/dl) and no decrease of proteinuria more than 50% after 6 months of conservative treatment with ACEi OR ARBs.

**Plus, one of the following:**

s. albumin >25g/dl., high titer of PLA2R antibodies, high urinary IgG alpha1 or B2 microglobulin.

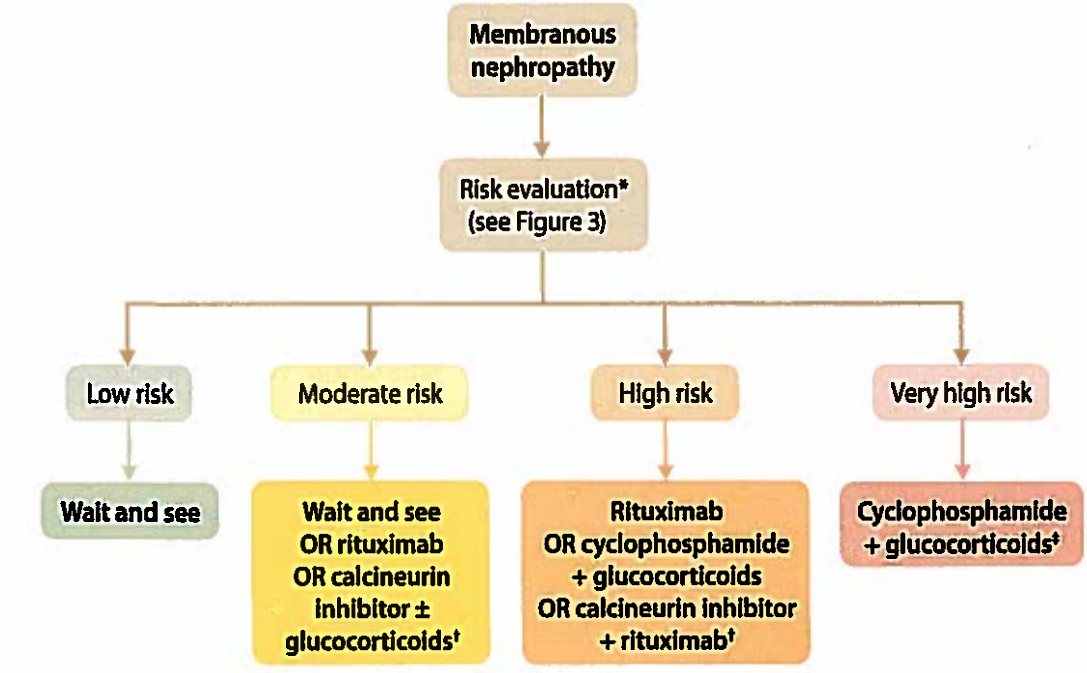
**Very high risk:**

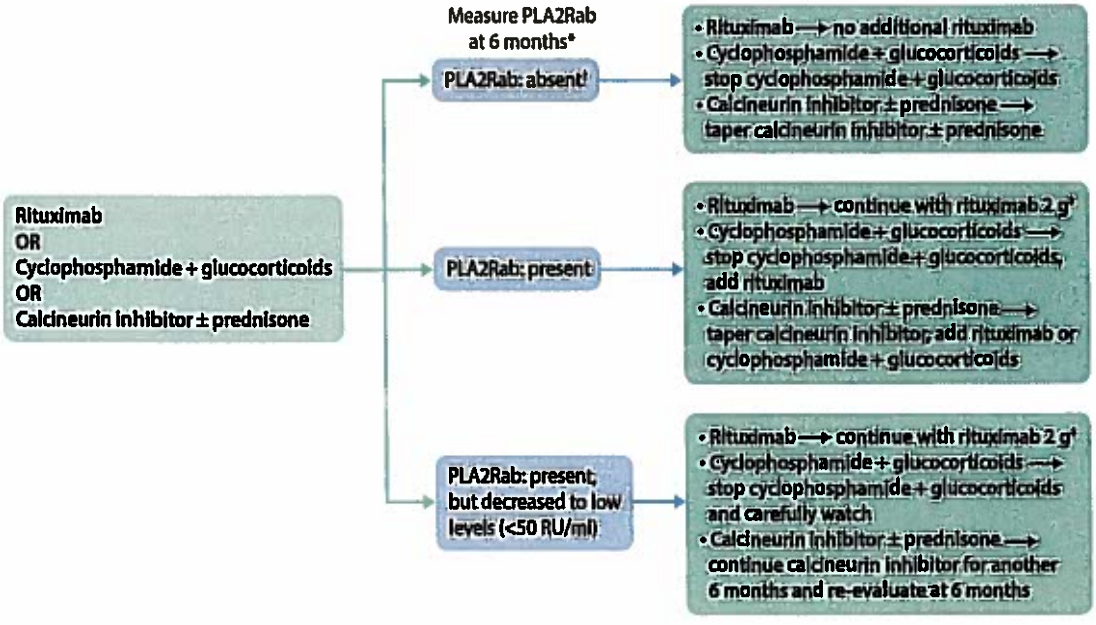
Life threatening nephrotic syndrome or rapid deterioration of kidney function not otherwise explained.

**Management:**

- **LOW RISK:** wait and see.
- **moderate risk**: wait and see or rituximab or cyclosporins +/- steroids.
- **high risk: rituximab or cyclosporins and rituximab or** cyclophosphamides and glucocorticoids.
- **very high risk:**
  Cyclophosphamide and glucocorticoids.

## SUMMARY OF TREATMENT


Membranous nephropathy
Risk evaluation* (see Figure 3)
Low risk
Moderate risk
High risk
Very high risk
Wait and see
Wait and see OR rituximab OR calcineurin inhibitor ± glucocorticoids†
Rituximab OR cyclophosphamide + glucocorticoids OR calcineurin inhibitor + rituximab†
Cyclophosphamide + glucocorticoids‡


Rituximab
OR
Cyclophosphamide + glucocorticoids
OR
Calcineurin inhibitor ± prednisone
Measure PLA2Rab at 6 months*
PLA2Rab: absent
PLA2Rab: present
PLA2Rab: present, but decreased to low levels (<50 RU/ml)
• Rituximab → no additional rituximab
• Cyclophosphamide + glucocorticoids → stop cyclophosphamide + glucocorticoids
• Calcineurin inhibitor ± prednisone → taper calcineurin inhibitor ± prednisone
• Rituximab → continue with rituximab 2 g†
• Cyclophosphamide + glucocorticoids → stop cyclophosphamide + glucocorticoids, add rituximab
• Calcineurin inhibitor ± prednisone → taper calcineurin inhibitor, add rituximab or cyclophosphamide + glucocorticoids
• Rituximab → continue with rituximab 2 g†
• Cyclophosphamide + glucocorticoids → stop cyclophosphamide + glucocorticoids and carefully watch
• Calcineurin inhibitor ± prednisone → continue calcineurin inhibitor for another 6 months and re-evaluate at 6 months

**EX:** Male pt. 50 years old chronic heavy smoker with several episodes of haemoptysis, he is grossly oedematous, ascites, Hb=10, Creatinine=180, albumin=22. Urine protein +++, 5 gm proteinuria/day **>>>? Bronchial carcinoma with membranous GN >> BX: thickened glomerular BM** with **deposits of IgG and C3.**

## IgA nephropathy

### Presentations:

- Young male (in their 20s and 30s.), 3 times more common in males.
- Recurrent episodes of macroscopic hematuria (The urine may be frankly bloody or may be the color of cola.
- There are no clots in the urine and the hematuria is generally painless although some patients complain of mild loin pain), It tends to settle spontaneously within 5 days although the episodes may be recurrent lasting for 1 to 2 years.

An RBC cast caused by bleeding into the tubule from the glomerulus. T hese casts are seen in glomerulonephritis, IgA nephropathy, lupus nephritis, G oodpasture syndrome, and Wegener granulomatosis. RBC casts are always pathologic

- Typically associated with mucosal infections within 24-48 hours e.g., URTI (sore throat, pharyngitis).
- It may also present with proteinuria, microscopic hematuria, renal failure or hypertension.
- Nephrotic range proteinuria can occur but rare in only 5%.
- Good prognosis is associated with normal BP, renal function and absence of proteinuria at presentation.

### Associated conditions:

- Alcoholic cirrhosis
- Coeliac disease/dermatitis herpetiformis

**IgA nephropathy (IgAN) is the most common pattern of primary glomerular disease worldwide and remains a leading cause of CKD and kidney failure.**

**Most commonly,**

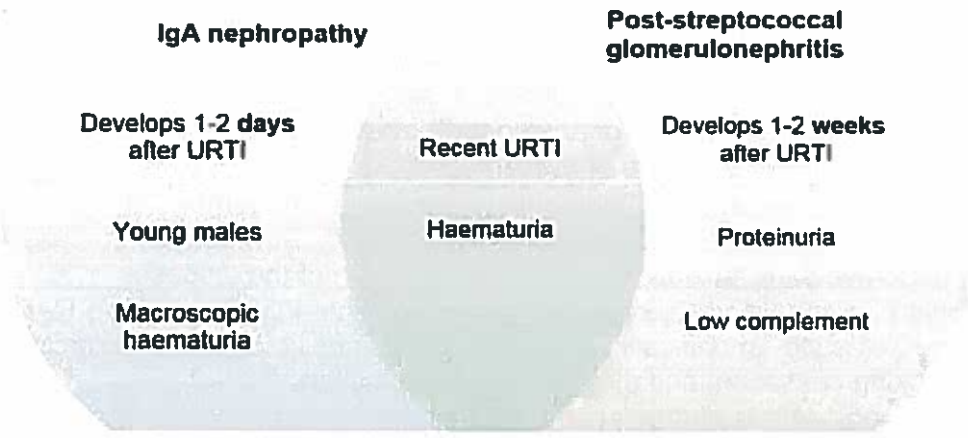
- **IgAN** is asymptomatic and follows a slowly progressive course with approximately 25%–30% of any cohort developing kidney
- failure within 20–25 years of presentation.
- **Unlike** the majority of glomerular diseases, management of IgAN is focused on non-immunosuppressive based strategies, so-called supportive care, to slow the rate of progression of the disease.
- This encompasses rigorous BP control, optimal inhibition of the RAS, and lifestyle modification, including weight reduction, exercise, smoking cessation, and dietary sodium restriction.
- Although IgAN is characterized by a single histopathologic criterion of predominant or codominant IgA deposits on kidney biopsy, it is now well recognized that this "disease" exhibits marked heterogeneity in its clinical and pathological features.
- There is good evidence that the epidemiology, clinical presentation, disease progression, and long-term outcome of IgAN differ across ethnic populations around the world.
- IgAN is most prevalent and more likely to cause kidney failure in people of East Asian ancestry, followed by Caucasians, and is relatively rare in individuals of African descent.
- It is unclear if these observations are due to differences in pathogenesis and/or the contribution of varying genetic and environmental influences.

## Pathophysiology

- thought to be caused by mesangial deposition of IgA immune complexes
- there is considerable pathological overlap with Henoch-Schonlein purpura (HSP)
- histology: **mesangial hypercellularity, positive immunofluorescence for IgA & C3**

## Differentiating between IgA nephropathy and post-streptococcal glomerulonephritis

- post-streptococcal glomerulonephritis is associated with low complement levels
- main symptom in post-streptococcal glomerulonephritis is proteinuria (although haematuria can occur)
- there is typically an interval between URTI and the onset of renal problems in post-streptococcal glomerulonephritis




## Diagnosis;

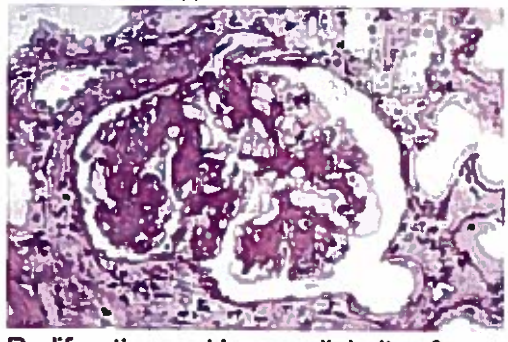
- Considerations for the diagnosis of immunoglobulin A nephropathy (IgAN):
- **IgAN** can only be diagnosed with a kidney biopsy.
- Determine the **MEST-C score (mesangial [M] and endocapillary [E] hypercellularity, segmental sclerosis [S], interstitial fibrosis/tubular atrophy [T], and crescents [C]) according to the revised Oxford Classification.**
- There are no validated diagnostic serum or urine biomarkers for **IgAN.** Assess all patients with **IgAN** for secondary causes.
- Prognosis Several prognostic scores have been developed to assist in predicting kidney outcomes in **IgAN**. Earlier scoring systems included a variety of pathologic classification schema

**More recently, the standardized MEST-C score as defined in the revised Oxford Classification has been incorporated into development of prognostic scoring systems and machine-learning used to select predictive variables.**

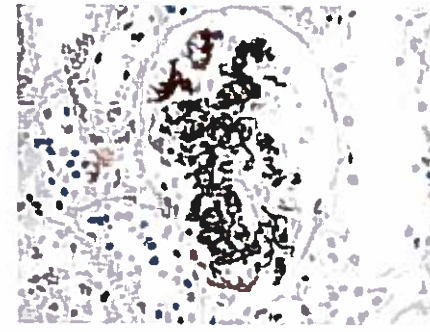
- The tool is available as an online calculator to assist in discussions with patients regarding outcome.
- Clinical and histologic data at the time of biopsy can be used to risk stratify patients.
- The International IgAN Prediction Tool is a valuable resource to quantify risk of progression and inform shared decision-making with patients.
- **Use Calculate by QxMD application for this purpose** There are no validated prognostic serum or urine biomarkers for IgAN other than eGFR and proteinuria.

## Prognosis:

- 30% of children will have a spontaneous remission within 10 years.
- 25% of patients develop ESRF within 20 years.
- Markers of good prognosis: frank haematuria.
- Markers of poor prognosis: male gender, proteinuria (especially > 2 g/day), hypertension, smoking, hyperlipidaemia, ACE genotype DD.
- Where ESRD does occur, renal transplantation carries a high chance of success.



Proliferation and hypercellularity of the mesangium is seen in the glomerulus



Immunostaining for IgA in a patient with HSP

## Treatment

**A.** Considerations for treatment of all patients with IgAN who do not have a variant form of primary IgAN .The primary focus of management should be optimized supportive care.

- forms of IgAN: IgA deposition with minimal change disease (MCD), IgAN with acute kidney injury(AKI), and IgAN with rapidly progressive glomerulonephritis (RPGN) may require specific immediate treatment.
- All patients have their blood pressure managed, as If the patient has proteinuria >0.5 g/d, we recommend that initial therapy be with either an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin II receptor blocker (ARB)
- This recommendation is based on an extensive body of evidence
- showing that hypertension and proteinuria are major risk factors for progression of CKD and that treatment of hypertension and reduction of proteinuria reduces the risk of progression to kidney
- **The data elements included in the International IgAN**
- **Prediction Tool.** Using clinical and histologic data at biopsy, users can determine a 50% decline in eGFR or kidney failure at selected time intervals.

- The tool is not validated for use with data obtained remotely from the time of biopsy. ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; GFR, glomerularfiltration rate; **MEST-C**, mesangial (M) and endocapillary (E) hypercellularity, segmental sclerosis (S), and interstitial fibrosis/ tubular atrophy (T) and creasents(C).

**B.** patients who remain at high risk of progressive CKD despite maximal supportive care be considered for a 6-month course of glucocorticoid therapy. The important risk of treatment-emergent toxicity must be discussed with patients, particularly those who have an eGFR <50 ml/min per 1.73 m2 .

**C.** Patients with rapidly progressive IgAN should be offered treatment with cyclophosphamide and glucocorticoids.

## Top 10 Takeaways for Clinicians from the KDIGO 2021 Clinical Practice Guideline for the Management of IgA Nephropathy

**1**

### Diagnosis of IgA nephropathy (IgAN)

IgAN can only be diagnosed with a kidney biopsy. There are no validated diagnostic serum/urine biomarkers. The differential diagnosis of IgA dominant glomerulonephritis includes primary IgAN, IgA vasculitis, cirrhosis, inammatory bowel disease and infection-related GN. (Figure 1)

**2**

### Prognosis

The International IgAN Prediction Tool helps determine the risk of a 50% decline in eGFR or progression to kidney failure up to 6.7 years from the time of kidney biopsy to inform shared decision-making with patients (available at QxMD1). (Figure 2) There are no validated prognostic serum/urine biomarkers other than eGFR and proteinuria.

**3**

### Treatment for all patients with primary IgAN

Initial management is supportive care including lifestyle modi-cation (smoking cessation, weight control, regular exercise and dietary sodium restriction), blood pressure control and maximum tolerated RAS blockade.

**4**

### Identification of patients at high risk of progression

Assess risk of progression regularly in all patients with IgAN. High risk is currently de-ned as persistent proteinuria >1 g/d despite 3 months of stable, optimized supportive care. While proteinuria reduction to under 1 g/d is a surrogate marker of improved kidney outcome in IgAN, persistent proteinuria 0.5–1 g/d is also likely to increase the risk of progression. (Figure 3)

**Management of high-risk patients on optimized supportive care**

5 Neither the International IgAN Prediction Tool nor the Oxford Classi-cation MEST-C score alone can be used to determine the likely impact of any particular treatment regimen. Unless inclusion in a clinical trial is possible, glucocorticoid therapy may reduce the risk of kidney failure in IgAN. If glucocorticoids are considered, the risk of treatment-emergent toxicity, in particular serious infectious complications, must be discussed with the patient, particularly those with an eGFR <50ml/min/1.73 m2. (Figure 3)

**Ethnicity-specific alternative treatment options**

6 There are data to support the use of mycophenolate mofetil (MMF) in Chinese patients as a glucocorticoid-sparing agent. Tonsillectomy is widely performed in Japan with supportive data for Japanese patients. (Figure 3)

**IgAN variants – rapidly progressive glomerulonephritis**

7 Rarely patients with IgAN can develop a rapidly progressive glomerulonephritis (RPGN) associated with extensive crescent formation. These cases should be treated with cyclophosphamide and glucocorticoids in the same way as ANCA-associated vasculitis. The presence of crescents in a kidney biopsy without a concomitant change in serum creatinine does not constitute a RPGN.

**IgAN variants – AKI and nephrotic syndrome**

8 Acute kidney injury can complicate episodes of severe visible hematuria. Treatment is supportive. IgAN rarely presents with nephrotic syndrome. In such cases, electron microscopy may be otherwise consistent with minimal change disease (MCD) and patients should be treated in accordance with the guidelines for MCD.

**IgAN in children**

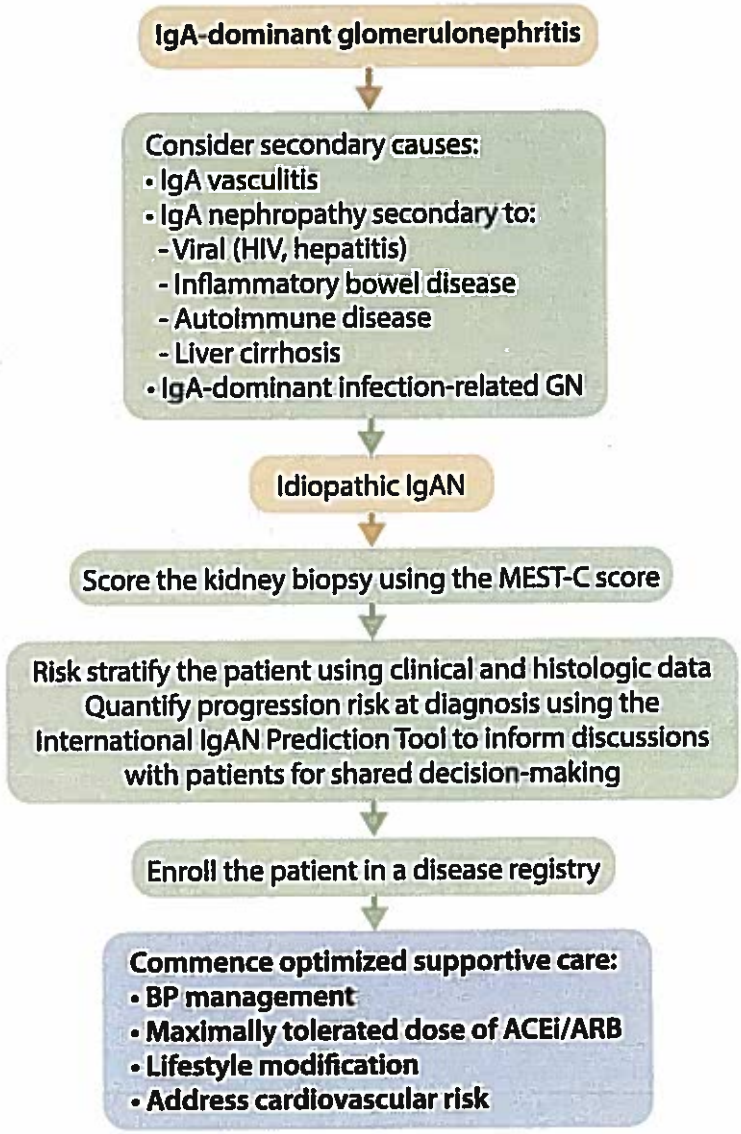
9 The International IgAN Prediction Tool has been validated for use in children. Management of children with IgAN is similar to adults except for a lower threshold for the early use of glucocorticoids. Long term follow-up is essential, even after complete remission, as children can relapse after many years of stable disease.

**10**

### IgA vasculitis

Diagnosis is often made on clinical criteria alone but a kidney biopsy should always be considered in patients with an RPGN, proteinuria >1 g/d, and/or impaired kidney function. Glucocorticoids should not be used to prevent nephritis in patients with isolated extrarenal IgAV. Management for adults and children should follow the guidance for IgAN.

Figure 1


IgA-dominant glomerulonephritis
Consider secondary causes:
• IgA vasculitis
• IgA nephropathy secondary to:
- Viral (HIV, hepatitis)
- Inflammatory bowel disease
- Autoimmune disease
- Liver cirrhosis
• IgA-dominant infection-related GN
Idiopathic IgAN
Score the kidney biopsy using the MEST-C score
Risk stratify the patient using clinical and histologic data
Quantify progression risk at diagnosis using the International IgAN Prediction Tool to inform discussions with patients for shared decision-making
Enroll the patient in a disease registry
Commence optimized supportive care:
• BP management
• Maximally tolerated dose of ACEi/ARB
• Lifestyle modification
• Address cardiovascular risk

| |
|---|
| **Estimated GFR at biopsy**.....ml/min/1.73 $m^2$ |
| **Systolic blood pressure at biopsy**.....mmHg |
| **Diastolic blood pressure at biopsy**.....mmHg |
| **Proteinuria at biopsy**.....g/day |
| **Age at biopsy**.....years |
| **Race**<br>Caucasian<br>Chinese<br>Japanese<br>Other |
| **Use of ACE inhibitor or ARB at the time of biopsy**<br>No<br>Yes |
| **MEST M-score**<br>0<br>1 |
| **MEST E-score**<br>0<br>1 |
| **MEST S-score**<br>0<br>1 |
| **MEST T-score**<br>0<br>1<br>2 |
| **Immunosuppression use at or prior to biopsy**<br>No<br>Yes |

**Figure 2**

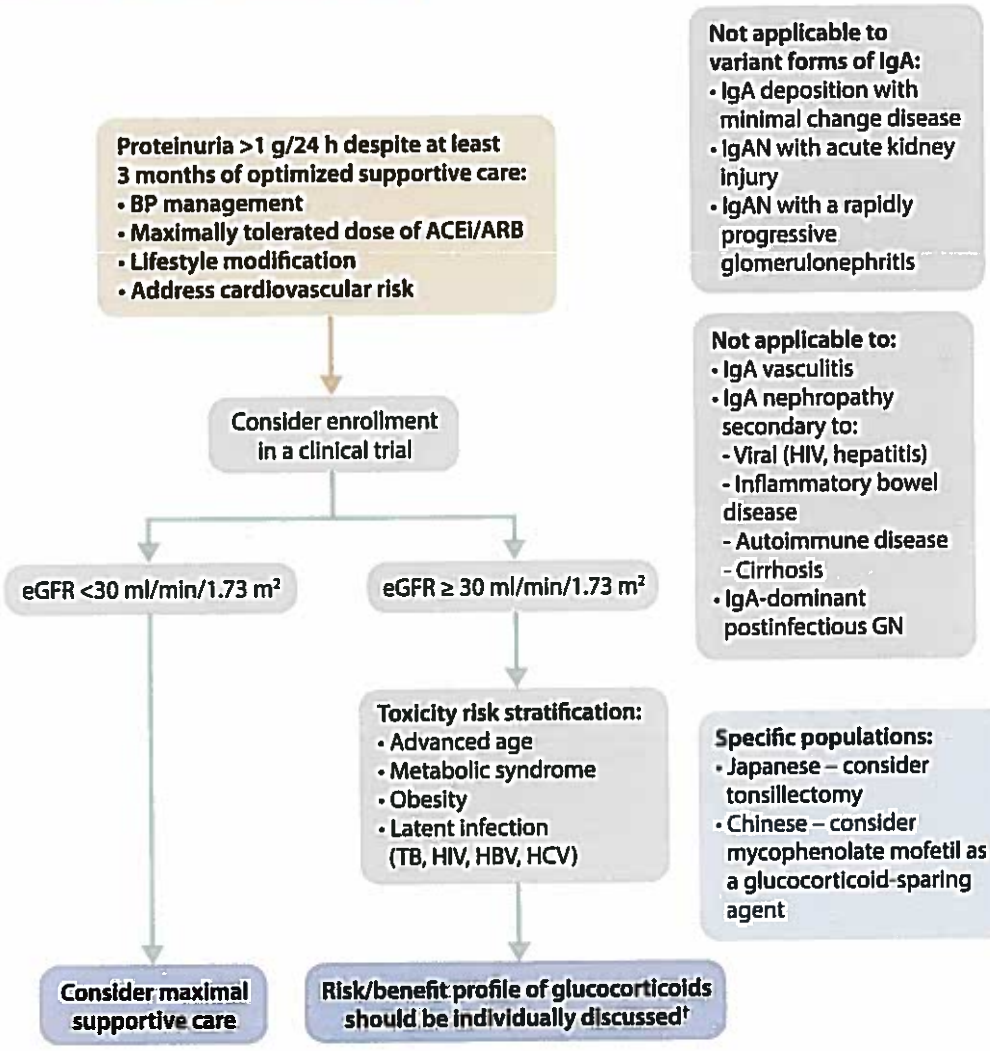

Not applicable to variant forms of IgA:
• IgA deposition with minimal change disease
• IgAN with acute kidney injury
• IgAN with a rapidly progressive glomerulonephritis
Proteinuria >1 g/24 h despite at least 3 months of optimized supportive care:
• BP management
• Maximally tolerated dose of ACEi/ARB
• Lifestyle modification
• Address cardiovascular risk
Not applicable to:
• IgA vasculitis
• IgA nephropathy secondary to:
- Viral (HIV, hepatitis)
- Inflammatory bowel disease
- Autoimmune disease
- Cirrhosis
• IgA-dominant postinfectious GN
Consider enrollment in a clinical trial
eGFR <30 ml/min/1.73 m²
eGFR ≥ 30 ml/min/1.73 m²
Toxicity risk stratification:
• Advanced age
• Metabolic syndrome
• Obesity
• Latent infection (TB, HIV, HBV, HCV)
Specific populations:
• Japanese – consider tonsillectomy
• Chinese – consider mycophenolate mofetil as a glucocorticoid-sparing agent
Consider maximal supportive care
Risk/benefit profile of glucocorticoids should be individually discussed†

**Figure 3**

- There is considerable pathological **overlap with HSP CALLED IgA VASCULITIS** (arthritis, rash, abdominal pain and nephritis).
- Biopsy: **Mesangial proliferation**.
- Histology:
  - **Light**: **Mesangial hypercellularity** and extracellular matrix expansion.
  - **E M**: Positive immunofluorescence for IgA & C3.

**Differentiating** between IgA nephropathy and ***post-streptococcal glomerulonephritis:***

- Post-streptococcal glomerulonephritis is associated with ***low*** complement levels (**C3**).
- Main symptoms in post-streptococcal glomerulonephritis is ***proteinuria*** (although hematuria can occur).
- There is typically an ***interval (weeks)*** (e.g.,**1 to 3 weeks**) between URTI and the onset of renal problems in post-streptococcal glomerulonephritis.
- ***Humps*** in the subepithelial space on electron microscopy. (NB: Not all cases of post-streptococcal GN require a biopsy).
- *A **wire-loop lesion*** is a capillary loop with immune complex deposition circumferential around the loop is seen by light microscopy.

**EX:** A **25**-year-old man developed **bilateral loin pain** and **frank haematuria.** His symptoms had started **24 hours after** developing a sore throat.
BP was 138/88 mmHg. Urinalysis was positive for blood (4+) and protein (2+).
The most likely diagnosis >>> **IgA nephropathy, NOT** post-strept GN

**EX:** A 26-year-old female who is **13 weeks pregnant** has a sustained **BP** of 170/92 mmHg. She has no past medical history of note and has otherwise been well and asymptomatic. This is her first pregnancy.

Examination is otherwise generally normal and no abnormalities are noted on fundoscopy. Ultrasound examination of the kidneys showed both kidneys to be of equal size of 9-10 cm. **Urinalysis reveals protein (+) and blood (+).**

What is the most likely cause of her hypertension >>> **IgA nephropathy.**
**TREATMENT: Oral labetalol** is the safest agent to use in the first and second trimester of pregnancy.
**Explanation:**
- At 13 weeks of pregnancy, it is too early to present with pre-eclampsia.
- Fibromuscular dysplasia does not typically present with dipstick haematuria.
- Membranous GN is associated with a nephrotic syndrome and therefore one would expect more proteinuria and no hematuria.
- This patient has normal sized kidneys, which would be unusual for reflux nephropathy.
- IgA nephropathy can present with all the above features.
- Beta blockers may cause intrauterine growth retardation.
- ACE inhibitors or ARBs may cause congenital abnormality.
- Manufacturers recommend avoidance of hydralazine.

**NB**: The most common cause of **macroscopic haematuria** in a **child** is **IgA** nephritis.
**NB**: In old patient >>> **Renal / bladder cancer.**

## Henoch-Schoenlein purpura (HSP)-IgA vasculitis

- Henoch-Schoenlein purpura (HSP) is an **IgA** mediated **small** vessel **vasculitis**.
- There is a degree of overlap with IgA nephropathy (Berger's disease).
- 90% of cases occur in children 2-10 years but can occur in **any age group**.
- HSP is usually seen in children following an infection such as group A Streptococci and Mycoplasma.
- In children, HSP is the most common cause of vasculitis affecting the kidneys.
- The diagnosis can be easily missed, a high degree of suspicion is required.

### Features

- **Palpable purpuric rash** (with localized oedema), due to cutaneous vasculitis, over buttocks and extensor surfaces of arms and legs.
- **Abdominal pain** due to gut vasculitis, which may be severe in some cases, leading **to bloody diarrhea**.
- **Polyarthritis**: especially large: Hips, ankles and knees.
- Features of **IgA** nephropathy may occur e.g., painless macroscopic/microscopic **hematuria, proteinuria, and renal failure.**

**Purpuric Eruptions**

## Treatment:

- HSP is a **self-limiting vasculitis**
- Treatment of nephropathy is generally **supportive**.
- All patients with HTN and/or proteinuria should be started on a **ACEIs**.
- Analgesia for arthralgia.
- Once the BP has been controlled or if there were worsening renal function or proteinuria, she should have a **renal biopsy**, and if this showed changes of a **crescentic** glomerulonephritis (GN), then an immunosuppression regime similar to that used in renal vasculitis should be started (probably with high dose steroids in the first instance +/- cyclophosphamide).
- There is inconsistent evidence for the use of steroids and immunosuppressant

## Prognosis:

- Usually **excellent, HSP is a self-limiting condition**, especially in children without renal involvement
- It usually settles between 4 to 6 weeks without sequelae if kidney involvement is mild.
- Around **1/3 rd.** of patients has a **relapse.**

### Glomerulonephritis and low complement (3)

**Immune complex Glomerulonephritides can be classified based on normal or decreased C3.**

Proteinuria points to glomerular pathology. Glomerular diseases with low complement levels narrow down the differential diagnosis.

**Disorders associated with glomerulonephritis and low serum complement levels:**

- **Post-infectious** glomerulonephritis (e.g., post streptococcal GN).
- Subacute bacterial **endocarditis** (Low C3 and C4).
- **SLE** (Low C3 and C4).
- **Mesangiocapillary (membranoproliferative)** GN (low C3, normal C4).
- **Cryoglobulinaemia** (Low C3 and C4).

**IgA nephropathy is with normal C3**

| | Postinfectious GN | Shunt nephritis | Endocarditis-related GN | IgA-dominant infection-related GN |
|---|---|---|---|---|
| **Risk and risk features** | Children, elderly, immunocompromised hosts, subsanitary living conditions | Highest: Ventriculo-atrial<br>Mid: Ventriculo-jugular<br>Least: Ventriculo-peritoneal | Prosthetic valve or structural heart valve lesion; substance abuse; elderly; diabetes mellitus; hepatitis C; HIV; immunocompromised host | Diabetes mellitus, hypertension, heart disease, malignancy, alcohol or substance abuse, or kidney transplantation |
| **History** | Seek evidence of antecedent resolved pharyngitis (1–2 wks) or impetigo (4–6 wks) | May present within months or decades of shunt placement, sometimes after shunt revision. Diagnosis may be confounded and difficult in the 40% with occult infection | Echocardiographic evidence of cardiac valvular vegetations | Demonstration of active blood or tissue infection in a patient with acute GN |
| **Physical exam** | In some, active skin or tonsil infections present | Non-specific signs/symptoms of infection, lethargy, fever, clinical signs of bacteremia | Fever, new or changed cardiac murmur; splenomegaly; characteristic skin lesions | Frequent hypertension. Exam mostly reflects the location/severity of the infection |
| **Laboratory kidney** | • Urinalysis (assess for glomerular hematuria and red blood cell casts); ACR; PCR<br>• Measure serum creatinine/eGFR | | | |
| **Laboratory infection** | Culture skin or tonsils if infected<br>Measure anti-streptolysin O, anti-DNAse B, and anti-hyaluronidase antibodies | Organism culture in blood, cerebrospinal fluid, shunt tip (after removal) | Blood culture positive 90–98%; negative 2–10%. Fastidious infections, such as *Candida*, *Coxiella burnetii*, *Borrelia*, and *Bartonella* may be difficult to culture. Serological tools for diagnosis may be required in such cases | Culture blood/tissues to identify bacterial infection (mostly staphylococcal) |
| **Laboratory immunology** | • Assess for low complement (C3, C4), rheumatoid factor, cryoglobulins, factor B antibody levels<br>• Rule out other causes of nephritis if diagnosis in doubt: ANA, ANCA (occasionally PR3-ANCA in shunt nephritis and endocarditis), anti-GBM antibody | | | |
| | | | | Serum IgA may be high |

Evaluation of classic bacterial infection-related GN syndromes. ACR, albumin-creatinine ratio; ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibody; eGFR, estimated glomerular filtration rate; GBM, glomerular basement membrane; GN, glomerulonephritis; HIV, human immunodeficiency virus; PCR, protein-creatinine ratio; PR3, proteinase 3.

## Goodpasture's syndrome (Anti-GBM Disease)

- Goodpasture's syndrome is **rare** condition associated with both pulmonary hemorrhage and rapidly progressive glomerulonephritis.
- Goodpasture's syndrome is more common in **men** (sex ratio 2:1) and has a **bimodal** age distribution (peaks in 20-30 and 60-70 age bracket).
- It is associated with HLA DR2 and HLA-B7.
- Although many diseases can present with these symptoms, the name Goodpasture's syndrome is usually reserved for the autoimmune disease triggered when the patient's immune system attacks **Goodpasture's antigen** (a **type II hypersensitivity reaction)** which is found in the kidney and lung causing damage to these organs.
- It is caused by anti-glomerular basement membrane **(anti-GBM) antibodies** against type **IV** collagen.
- 30% of patients had positive ANCA serology (**p-ANCA** and is directed against myeloperoxidase).

### Features:

- Pulmonary hemorrhage, hemoptysis.
- Followed by **RPGN (crescentic)**

**Factors which increase likelihood of pulmonary hemorrhage:**

- Young males
- Smoking
- Lower respiratory tract infection
- **Pulmonary Oedema.**
- **Inhalation of hydrocarbons.**

### Investigations:

- Renal biopsy: **linear IgG deposits** along basement membrane.
- **Raised transfer factor** secondary to pulmonary hemorrhages.
- **Lung biopsy:** accumulation of hemosiderin laden macrophages with alveoli.

### Management:

Where there is **severe hemoptysis, rapid removal of Anti-GBM antibody** is indicated, and the **best** way to do this is by **Plasmapharesis** at a specialist center and this is usually **accompanied by pulse therapy of IV methylprednisolone and cyclophosphamide.**

- **Plasma exchange**: daily or on alternate days for 2 to 3 weeks, this will remove the circulating antibody, response is assessed by monitoring symptoms and anti-GBM antibody titers , plasma pheresis should continue till the antibodies disappear.

- Immunosuppressants by **Steroids** and **Cyclophosphamide** for 6 to 9 months following remission.
- High dose pulsed methylprednisolone is instituted alongside or soon after plasma exchange has been commenced. This is then followed by cyclophosphamide therapy and high dose oral prednisolone which is very gradually weaned to a lower maintenance dose.
- Rituximab in refractory GBS.
- No maintenance therapy of anti-GBM disease is necessary.

**NB:**

- The combination of **hemoptysis, renal failure** and **linear IgG deposits** points to a diagnosis of Goodpasture's syndrome.
- The **ANCA**-related nephropathies are associated with **crescentic** glomerulonephritis.
- **Pulmonary Oedema** is associated with high risk; but **Dehydration** may ↓ the likelihood of pulmonary hemorrhage.
- Studies reveal that without treatment mortality is as high as 90%.
- Despite treatment the mortality of Goodpasture's is 11% and it has a high morbidity with 60% of patients becoming dependent on dialysis.
- Patients who have lost more than 50% of their renal function at diagnosis, unfortunately progress to long-term renal replacement therapy.

KDIGO 2021 guidelines recommend
Initiating immunosuppression with cyclophosphamide and glucocorticoids plus plasmapheresis in all patients with anti-GBM GN except those who are treated with dialysis at presentation, have 100% crescents or >50% global glomerulosclerosis in an adequate biopsy sample, and do not have pulmonary hemorrage.

**Goodpasture's syndrome:**
- Anti-GBM Abs.
- IgG deposits.

## Wegener's granulomatosis (WG)= granulomatous polyangiitis

Wegener's granulomatosis is a **multi-organ** autoimmune condition, which can be **fatal**, associated with a **necrotizing granulomatous vasculitis**, affecting both the **upper** and **lower** respiratory tract as well as the **kidneys**.
It is **rare** with an incidence of 5-10 per million.

### The classical triad consists of:

1) **Necrotising granulomatous inflammation** of the **respiratory tract**.
2) **Glomerulonephritis** and
3) A **small-vessel vasculitis**.

**Pulmonary** involvement is seen in 95% of cases, and **renal** involvement in 85% of cases.

## Features:

- Upper respiratory tract: **epistaxis**, **sinusitis**, nasal crusting.
- Lower respiratory tract: **dyspnea**, **hemoptysis**.
- Saddle-shape nose deformity.
- RPGN ('pauci-immune', 80% of patients).
- Also: vasculitis rash, eye involvement (e.g., proptosis), cranial nerve lesions.

## Common manifestations of Wegener's granulomatosis include:

- **Constitutional** symptoms like fevers, night sweats, fatigue, lethargy, weight loss, and arthralgia.
- **Ocular** involvement including conjunctivitis, Episcleritis, uveitis, optic nerve vasculitis, and **proptosis.**
- **ENT** symptoms like chronic sinusitis, rhinitis, otitis media and hearing loss, subglottic stenosis (leading to stridor and features of extra thoracic airway obstruction on flow-volume loop).
- **Pulmonary** disease, for example, pulmonary infiltrates, cough, hemoptysis, chest discomfort, and dyspnea.
- **Renal** disease manifests as **crescentic necrotizing glomerulonephritis.**
- **Nervous** system involvement manifests as mononeuritis multiplex, sensorimotor polyneuropathy, cranial nerve palsies, and vasculitis of small to medium-sized vessels of the brain or spinal cord, and granulomatous masses that involve the orbit, optic nerve, meninges or brain.
- **Skin** involvement can lead to palpable purpura or skin ulcers.

## Investigations:

- Positive ANA.
- **C -ANCA** positive in > **90%**, **P-ANCA** positive in 25%.
- Chest x-ray: wide variety of presentations, including cavitating lesions.
- Renal biopsy: epithelial **crescents** in Bowman's capsule.
- To confirm the diagnosis of pulmonary hemorrhage, ↑ raised KCO.

A **renal biopsy** confirms the diagnosis, and guides treatment, and should be performed prior to starting any long-term treatment.
**IV pulse methylprednisolone** may be commenced prior to renal biopsy if clinically necessary.

## Management:

**KDIGO 2021 recommend** initiating immunosuppression with cyclophosphamide and glucocorticoids plus plasmapheresis in all patients with anti-GBM GN except those who are treated with dialysis at presentation, have 100% crescents or >50% global glomerulosclerosis in an adequate biopsy sample, and do not have pulmonary hemorrhage.

**KDIGO ALSO** recommend considering conservative approach in patients without alveolar hemorrhage but who are oliguric and/or have advanced renal failure requiring dialysis especially with high proportion of crescents(80-100%) on renal biopsy.

- In patients who are unable to tolerate cyclophosphamides, **azathioprine** or **methotrexate** may be considered as alternatives.
- IV pulse steroid therapy is later converted to oral prednisolone and a suitable steroid sparing agents.
- Patients on high dose steroid and cyclophosphamide are at increased risk of pneumocystis pneumonia, so **co-trimoxazole** should be considered.

**alternatives**

- IVIG.
- TNF-alpha blocking agents, anti-thymocyte globulin (TTG) and monoclonal anti T-cell antibodies can be used in disease refractory to these agents.
- Rituximab IV (anti CD 20 antibody): in cases of resistant to medical treatment.
- Median survival = 8-9 years.

**NB:** The combination of pulmonary and renal involvement combined with a history of chronic sinusitis points towards a diagnosis of Wegener's granulomatosis.

NB: A prolonged history of epistaxis or sinusitis is commonly found in Wegener's granulomatosis, which in some patients is also associated with an eosinophilia.

# RPGN & RENAL VASCULITIS

## RPGN (Rapidly progressive Glomerulonephritis)

It is a disease of the kidney that results in a **rapid decrease in GFR** of at least **50%** over a **short period** (a **few days** to 3 months).

The incidence in UK is about **2** cases per **100,000** persons.

The main pathological finding is **fibrinoid necrosis > 90% of biopsy specimens** with extensive **crescent** formation in at least **50%** of the glomeruli.

These **crescents** are collections of **epithelial cells** and **macrophages proliferation** within the Bowman's space.

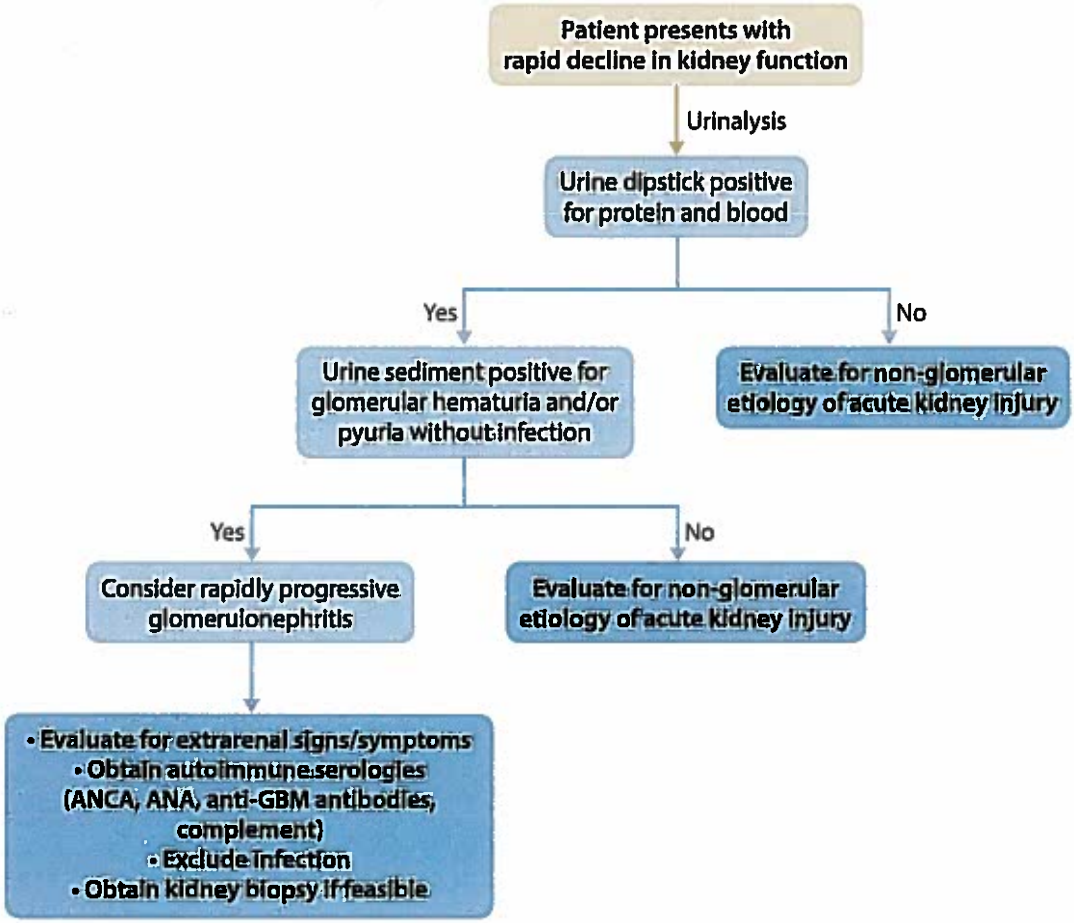
The presence of crescents indicates that **glomerular damage** is rapid and progressive (from onset to ESRD within weeks to months).

The clinical presentation is similar to other GNs, but there is rapid progression to renal failure.

**Immunofluorescence** detects deposits of **IgG** and **C3** in the **glomerular BM**.

There are **3 distributions** of immunofluorescence in crescentic GN:

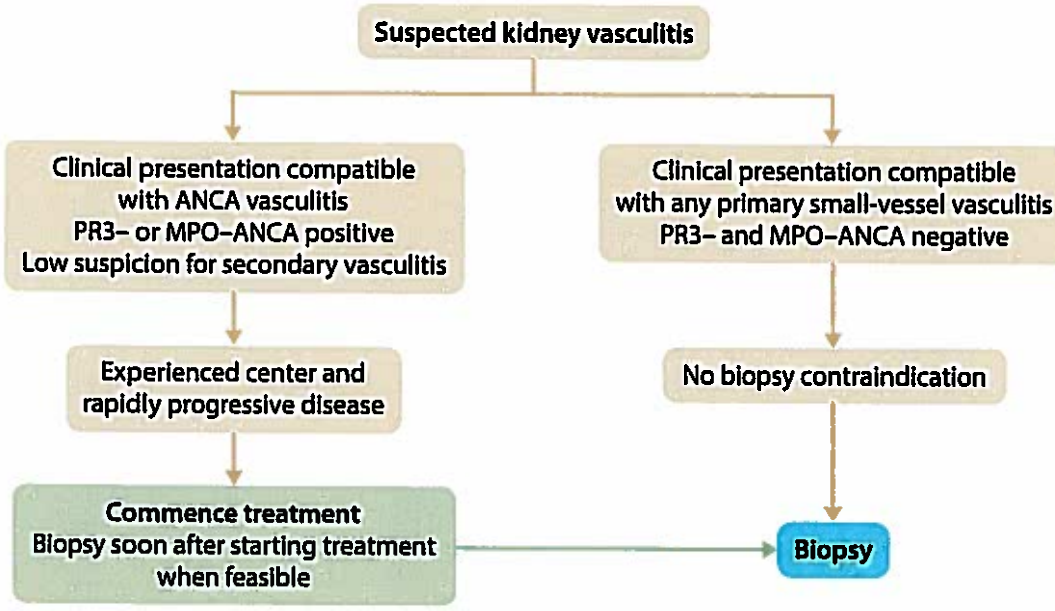
1) **Absent** immunofluorescence.
2) **Granular** immunofluorescence.
3) **Linear** immunofluorescence.


Patient presents with rapid decline in kidney function
Urinalysis
Urine dipstick positive for protein and blood
Yes
No
Urine sediment positive for glomerular hematuria and/or pyuria without infection
Evaluate for non-glomerular etiology of acute kidney injury
Yes
No
Consider rapidly progressive glomerulonephritis
Evaluate for non-glomerular etiology of acute kidney injury
• Evaluate for extrarenal signs/symptoms
• Obtain autoimmune serologies (ANCA, ANA, anti-GBM antibodies, complement)
• Exclude infection
• Obtain kidney biopsy if feasible

Diagnostic strategy in rapidly progressive glomerulonephritis. ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibody; GBM, glomerular basement membrane.

**Classification of RPGN is as follows:**

| Pauci-immune RPGN | Immune complex RPGN | Anti-GBM mediated RPGN |
|---|---|---|
| ➢ Microscopic polyangiitis.<br>➢ Wegener's granulomatosis.<br>➢ Idiopathic crescentic GN. | ➢ GN.<br>➢ SLE.<br>➢ Cryoglobulinemia<br>➢ IEC.<br>➢ HBV. | ➢ Anti-GBM GN (without lung Hge).<br>➢ Goodpasture's disease (with lung Hge). |


Suspected kidney vasculitis
Clinical presentation compatible with ANCA vasculitis PR3– or MPO–ANCA positive Low suspicion for secondary vasculitis
Clinical presentation compatible with any primary small-vessel vasculitis PR3– and MPO–ANCA negative
Experienced center and rapidly progressive disease
No biopsy contraindication
Commence treatment Biopsy soon after starting treatment when feasible
Biopsy

**Biopsy strategy in suspected kidney vasculitis. ANCA, antineutrophil cytoplasmic antibody; MPO, myeloperoxidase; PR3, proteinase 3.**

**Treatment: Pulse methylprednisolone IV and cyclophosphamide.**

**Early initiation** of high dose of steroids has been associated with improved mortality and more rapid return of kidney function.

Prognosis is **poor** if **initial creatinine > 600 Mmol/l.**

| Rituximab preferred | Cyclophosphamide preferred |
|---|---|
| • Children and adolescents<br>• Pre-menopausal women and men concerned about their fertility<br>• Frail older adults<br>• Glucocorticoid-sparing especially important<br>• Relapsing disease<br>• PR3–ANCA disease | • Rituximab difficult to access<br>• Severe GN (SCr >4 mg/dl [354 µmol/l]), combination of two intravenous pulses of cyclophosphamide with rituximab can be considered |

Factors for consideration when choosing between rituximab and cyclophosphamide for induction therapy of AAV. AAV, ANCA-associated vasculitis; ANCA, antineutrophil cytoplasmic antibody; GN, glomerulonephritis; PR3, proteinase 3; S Cr, serum creatinine.

# Amyloidosis

## Overview

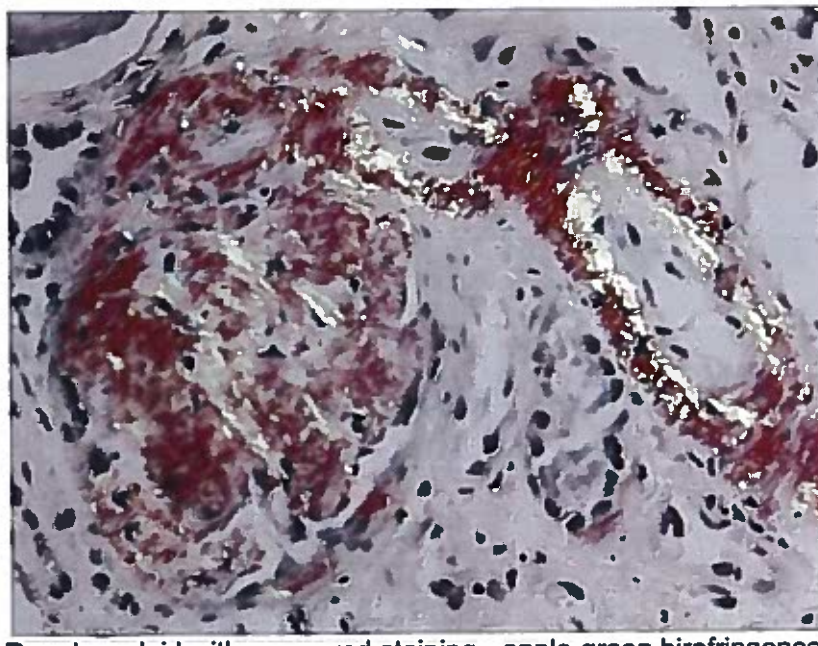
- amyloidosis is a term which describes the extracellular deposition of an insoluble fibrillar protein termed amyloid
- amyloid is derived from many different precursor proteins
- in addition to the fibrillar component, amyloid also contains a non-fibrillary protein called amyloid-P component, derived from the acute phase protein serum amyloid P
- other non-fibrillary components include apolipoprotein E and heparan sulphate proteoglycans
- the accumulation of amyloid fibrils leads to tissue/organ dysfunction

## Classification

- systemic or localized
- further characterised by precursor protein (e.g. AL in myeloma - A for Amyloid, L for immunoglobulin Light chain fragments)

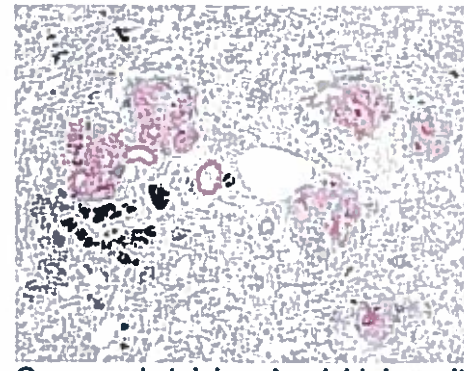
## Diagnosis

- **Congo red staining: apple-green birefringence**
- serum amyloid precursor (SAP) scan
- biopsy of skin, rectal mucosa, or abdominal fat



Renal amyloid with congo red staining - apple-green birefringence

Renal amyloid with congo red staining - apple-green birefringence



Congo red staining. Amyloid deposits are seen in both the arteries/arterioles and within the glomerulus. The deposit of amyloid within the mesangium is not dissimilar to the nodular lesions seen in diabetic nephropathy

## Amyloidosis: types

### AL amyloidosis

- the most common form of amyloidosis
- L for immunoglobulin Light chain fragment
- due to myeloma, Waldenstrom's, MGUS
- features include: nephrotic syndrome, cardiac and neurological involvement, macroglossia, periorbital eccymoses

### AA amyloid

- A for precursor serum amyloid A protein, an acute phase reactant
- seen in chronic infection/inflammation
- e.g., TB, bronchiectasis, rheumatoid arthritis
- features: renal involvement most common feature

### Beta-2 microglobulin amyloidosis

- precursor protein is beta-2 microglobulin, part of the major histocompatibility complex
- associated with patients on renal dialysis

## HIV Nephropathy

- Renal involvement in HIV patients may occur as a consequence of treatment or the virus itself.
- Protease inhibitors such as indinavir can precipitate intratubular crystal obstruction.
- HIV-associated nephropathy (**HIVAN**) accounts for up to **10%** of ESRD cases in the United States.
- Antiretroviral therapy has been shown to alter the course of the disease.

**There are five key features of HIVAN:**

- **FSGS:** with focal or global capillary collapse on renal biopsy.
- **Nephrotic range proteinuria**
- Normal or large kidneys by US.
- **↑ urea and creatinine**
- **Normotension**

It is surprisingly the BP of patients with HIV nephropathy is usually normal.

## Hemolytic uremic syndrome (HUS)

HUS is generally seen in **young adults** and produces a **triad** of:

- Acute renal failure >> Approximately 5% of patients will develop ESRD
- Microangiopathic haemolytic anaemia
- Thrombocytopenia with normal clotting

### Causes:

- **Post-dysentery (bloody Diarrhea):** classically **E coli 0157:H7** ('Vero-toxigenic', 'entero-haemorrhagic' E-coli) or Shigella dysentery.
- Tumours
- Pregnancy
- Cyclosporine, the Pill
- SLE
- HIV

HUS is characterized by the **sudden onset** of hemolytic anemia with fragmentation of red blood cells, thrombocytopenia and acute renal failure **after a prodromal illness of acute gastroenteritis often with bloody diarrhea.**

In HUS **90%** of patients are **children** and a history of **prodromal diarrhoeal** illness is more common.

Toxins produced in the intestine **enter the blood and bind to endothelial cells** in target organs.

**Endothelial cell damage** leads to platelet and fibrin deposition with resultant fragmentation of circulating red blood cells and microvascular occlusion.

**Neurological complications** include (from **confusion** to convulsion and coma): **Stroke, seizure** and **coma** occur in **25%** of patients.

Rarely pancreatitis, and Pleural and pericardial effusions.

## Investigations:

- **Fragmented RBCs on blood film**: (**schistocytes**, acanthocytes, burr cells, helmet cells, etc.).
- CBC: anemia, thrombocytopenia,
- U&E: acute renal failure
- Stool culture for E-coli

## Management:

- Treatment is **supportive** e.g. Fluids, blood transfusion, ttt of hypertension and dialysis if required.
- There is **no** role for antibiotics, despite the preceding diarrheal illness in many patients.
- The indications for plasma exchange in HUS are complicated. **As a general** rule **plasma exchange** is **reserved** for **severe** cases of HUS **not** associated with diarrhea.
- eculizumab (a C5 inhibitor monoclonal antibody) has evidence of greater efficiency than plasma exchange alone in the treatment of adult atypical HUS

> ➢ There is **no** role for antibiotics, steroids or immunosuppressant in HUS.
> ➢ **Plasma exchange** may be indicated, particularly in **severe** cases of HUS **not associated with diarrhoea.**

## Major differential diagnosis is:

- **Sepsis with DIC** - presents with abnormalities of **clotting** parameters.
- **TTP** (Thrombotic Thrombocytopenic Purpura) presents with **pentad** of:
  - Microangiopathic hemolytic anemia,
  - Thrombocytopenic purpura,
  - **Neurologic** abnormalities,
  - **Fever,** and
  - Renal disease.

Thrombotic thrombocytopenic purpura (TTP) and haemolytic uraemic syndrome (HUS) have **overlapping** clinical features and are part of the same spectrum of **microangiopathic disease**, with up to 60% of TTP patients missing at least one component of the classical pentad, and around 30% of HUS patients having neurological symptoms and fever.

Although once considered variants of a single syndrome, recent evidence suggests that the **pathogenesis of TTP** and **HUS is different.**

Patients with **TTP** there is **lack a plasma protease (↓ADAMS TS 13)** that is responsible for the **breakdown of von Willebrand factor (vWF) multimers** and these accumulate in the plasma. The activity of this protease is normal in patients with HUS.

Until the **test for vWF protease activity** becomes available, differentiation between HUS and TTP is based on the presence of **CNS** involvement in **TTP** and the **more severe renal involvement in HUS.**

**Children** account for **90%** of the cases of **HUS**, while **adults** are more frequently affected with **TTP.**

The **prognosis** is **worse** in **TTP** compared to HUS.

The therapy of choice for **TTP** is **plasma exchange with FFP.**

**Platelets transfusion is not recommended as it increase aggregations.**

## Plasma exchange (Plasmapheresis)

**Indications** for plasma exchange:

- **Guillain-Barre syndrome**
- **Myasthenia** gravis
- Chronic inflammatory demyelinating polyneuropathy (CIDP).
- **Goodpasture's** syndrome
- ANCA positive vasculitis e.g. **Wegener's, Churg-Strauss**
- **TTP/HUS**
- **Cryoglobulinemia**
- **Hyperviscosity** syndrome e.g. secondary to myeloma.
- Fulminant Wilson disease.

In most conditions **5% albumin** is the plasma substitute of choice (to reduce the risk of pathogen transmission), **except for TTP we should use FFP** where it has a therapeutic role in replacing the missing factor, ADAMTS-13.

### Complications of plasma exchange

- **hypocalcaemia:** due to the presence of citrate used as an anticoagulant for the extracorporeal system
- metabolic alkalosis
- removal of systemic medications
- coagulation factor depletion
- immunoglobulin depletion

# SLE Kidney

Lupus nephritis is a severe manifestation of systemic lupus erythematosus (SLE) that can result in end-stage renal disease.
SLE patients should be monitored by performing urinalysis at regular check-up appointments to rule out proteinuria.

## WHO classification

- **class I:** normal kidney
- **class II:** mesangial glomerulonephritis
- **class III:** focal (and segmental) proliferative glomerulonephritis
- **class IV:** diffuse proliferative glomerulonephritis
- **class V:** diffuse membranous glomerulonephritis
- **class VI:** sclerosing glomerulonephritis

**Class IV** (diffuse proliferative glomerulonephritis) is the most common and severe form. Renal biopsy characteristically shows the following findings:

- glomeruli shows endothelial and mesangial proliferation, 'wire-loop' appearance
- if severe, the capillary wall may be thickened secondary to immune complex deposition
- electron microscopy shows subendothelial immune complex deposits
- granular appearance on immunofluorescence

Diffuse proliferative SLE. Proliferation of endothelial and mesangial cells. The thickening of the capillary wall results in a 'wire-loop' appearance. Some crescents are present.

## Management

- treat hypertension
- initial therapy for focal (class III) or diffuse (class IV) lupus nephritis
  - glucocorticoids with either mycophenolate or cyclophosphamide
- subsequent therapy
  - mycophenolate is generally preferred to azathioprine to decrease the risk of developing end-stage renal disease

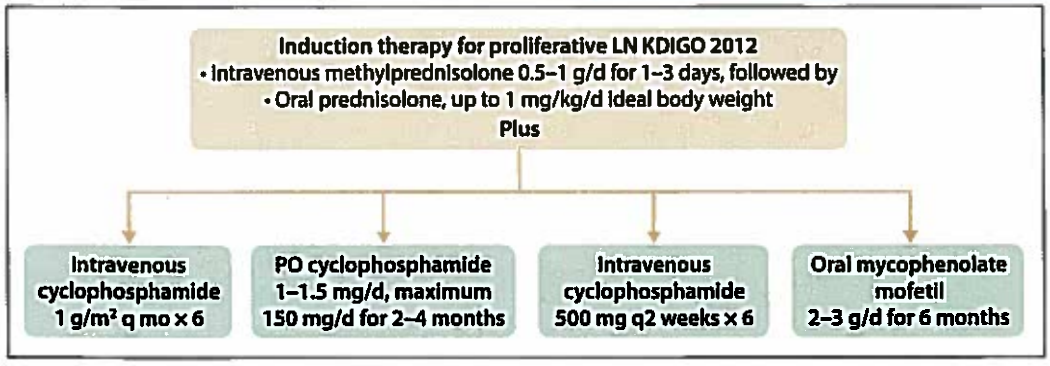
Diffuse proliferative glomerulonephritis (**Class 4**) (**IV**) is the **most common** and **severe** form of renal disease in SLE patients.
It also carries the **worst prognosis** for progression to renal failure.
**Treatment: high dose steroids** and **pulses of IV cyclophosphamide**, initially given monthly for 6 months and then quarterly.
Pulsed IV cyclophosphamide appears to be as effective as oral cyclophosphamide but has lower toxicity.

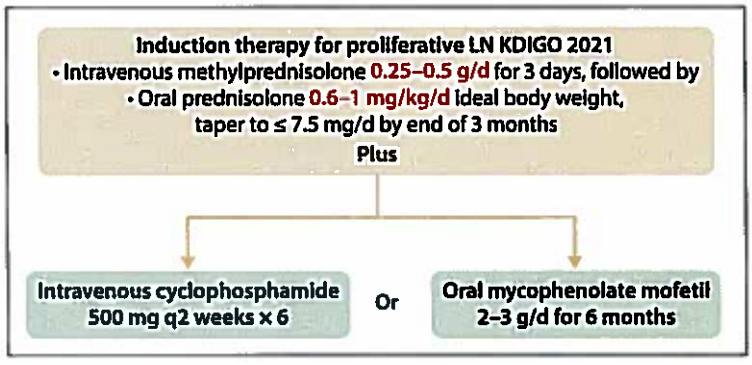
## Renal biopsy characteristically shows the following findings:

- Glomeruli shows endothelial and mesangial cells proliferation, 'wire-loop' appearance.
- If severe, the capillary wall may be thickened secondary to immune complex deposition.
- Electron microscopy >> shows subendothelial immune complex deposits
- Immunofluorescence >> granular appearance

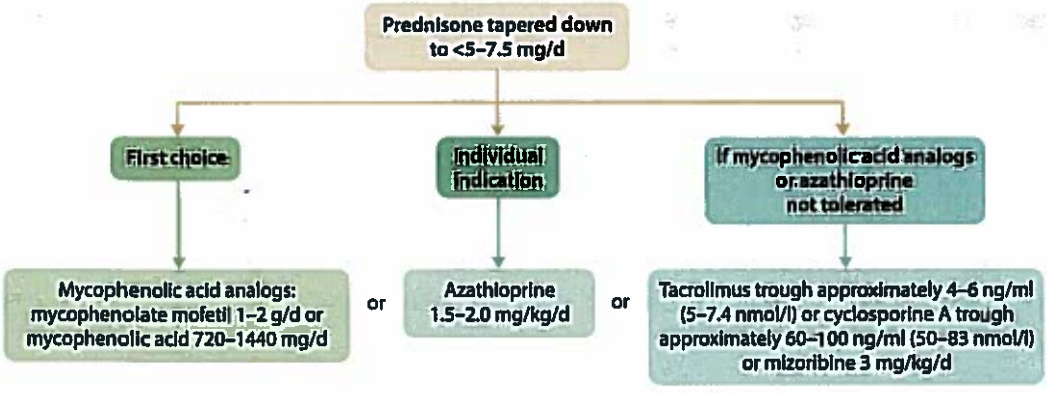
**Management:**

- Treat hypertension
- Corticosteroids if clinical evidence of disease
- Immunosuppressants: e.g.mycophenolate mofetil azathioprine/cyclophosphamide
- **In 2020 EULAR – the European Alliance of Associations for Rheumatology – and the European Renal Association (ERA) published updated treatment recommendations for LN.**
  - The outline targeted reductions in proteinuria over the course of the first year of therapeutic intervention.
  - Dr Hans-Joachim Anders reported on a post-hoc analysis of pooled **voclosporin** data from the AURA-LV and AURORA-1 studies based on these updated response criteria. The novel calcineurin inhibitor **voclosporin** was approved in 2021 in the USA for the treatment of adult patients with active LN in combination with background immunotherapy.
  - Within the first 3 months of treatment, 78.4% of patients on **voclosporin** and 62.4% in the control group achieved ≥25% reduction in urine protein creatinine ratio (UPCR). After 12 months, 52.6% and 33.1% of those receiving **voclosporin** and control, respectively, had achieved UPCR ≤0.7 mg/mg.
  - **The results suggest that addition of voclosporin to a background regimen of mycophenolate mofetil and low-dose steroids in patients with LN significantly increased the likelihood of achieving the UPCR targets of therapy recommended by EULAR/ERA.**

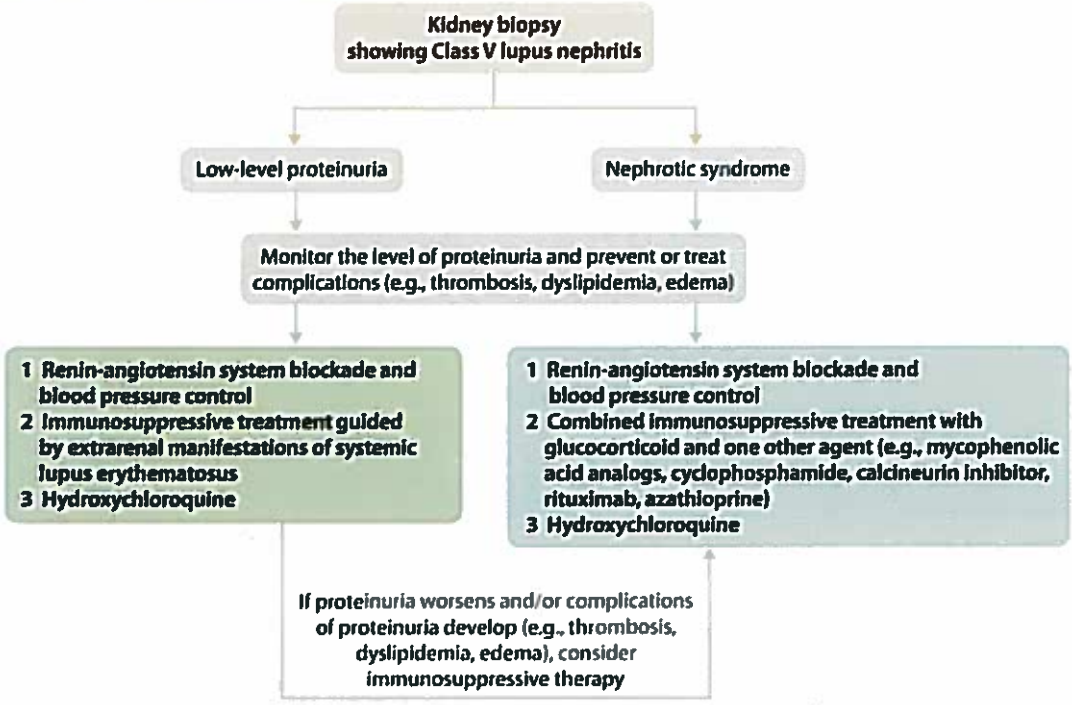

Induction therapy for proliferative LN KDIGO 2012
• Intravenous methylprednisolone 0.5–1 g/d for 1–3 days, followed by
• Oral prednisolone, up to 1 mg/kg/d ideal body weight
Plus
Intravenous cyclophosphamide 1 g/m² q mo × 6
PO cyclophosphamide 1–1.5 mg/d, maximum 150 mg/d for 2–4 months
Intravenous cyclophosphamide 500 mg q2 weeks × 6
Oral mycophenolate mofetil 2–3 g/d for 6 months


Induction therapy for proliferative LN KDIGO 2021
• Intravenous methylprednisolone 0.25–0.5 g/d for 3 days, followed by
• Oral prednisolone 0.6–1 mg/kg/d ideal body weight,
taper to ≤ 7.5 mg/d by end of 3 months
Plus
Intravenous cyclophosphamide 500 mg q2 weeks × 6
Or
Oral mycophenolate mofetil 2–3 g/d for 6 months

Comparison of recommended initial first-line treatment of proliferative LN in the 2012 versus KDIGO 2021 guideline. LN, lupus nephritis; mo, month; q2, every 2.


Prednisone tapered down to <5–7.5 mg/d
First choice
Individual indication
If mycophenolic acid analogs or azathioprine not tolerated
Mycophenolic acid analogs: mycophenolate mofetil 1–2 g/d or mycophenolic acid 720–1440 mg/d
or
Azathioprine 1.5–2.0 mg/kg/d
or
Tacrolimus trough approximately 4–6 ng/ml (5–7.4 nmol/l) or cyclosporine A trough approximately 60–100 ng/ml (50–83 nmol/l) or mizoribine 3 mg/kg/d

Maintenance therapy for Class III and Class IV LN. The target ranges for CNIs have been based on the transplant literature. The KDIGO Work Group acknowledges that targets for glomerular diseases are not known. Most clinicians check these levels to verify adherence and avoid CNI toxicity. At present, the most reasonable dosing of a CNI may be to titrate in the individual patient to obtain the desired effect on proteinuria, balancing dose escalation against serum creatinine and reducing the dose if serum creatinine increases but does not plateau or increases over 30% of baseline. If the serum creatinine level does not fall after dose reduction, the CNI should be discontinued. CNI, calcineurin inhibitor; LN, lupus nephritis.


Kidney biopsy showing Class V lupus nephritis
Low-level proteinuria
Nephrotic syndrome
Monitor the level of proteinuria and prevent or treat complications (e.g., thrombosis, dyslipidemia, edema)
1 Renin-angiotensin system blockade and blood pressure control
2 Immunosuppressive treatment guided by extrarenal manifestations of systemic lupus erythematosus
3 Hydroxychloroquine
1 Renin-angiotensin system blockade and blood pressure control
2 Combined immunosuppressive treatment with glucocorticoid and one other agent (e.g., mycophenolic acid analogs, cyclophosphamide, calcineurin inhibitor, rituximab, azathioprine)
3 Hydroxychloroquine
If proteinuria worsens and/or complications of proteinuria develop (e.g., thrombosis, dyslipidemia, edema), consider immunosuppressive therapy

Management of patients with pure Class V LN. LN, lupus nephritis.

## Diabetic Nephropathy (diabetic kidney disease)

Please refer to KDIGO GUIDELINES IN CKD AND TYPE 2 DIABETES 2020

**Described as:** a set of characteristic clinical and pathological findings such as albuminuria and progressive chronic kidney disease with hematuria sometimes.

It is the most common cause of nephrotic syndrome.

Normal urine albumin is less than 30 mg/ day. moderate increase is between 30-300 mg/day. sever increase is greater than 300mg/day.

### Stages:

**Stage 1:**

- **Hyperfiltration**: increase in GFR
- May be reversible

**Stage 2 (silent or latent phase):**

- Most patients do **not** develop microalbuminuria **for 10 years**
- GFR remains elevated

**Stage 3 (incipient nephropathy):**

- **Microalbuminuria** (albumin excretion of 30 - 300 mg/day, dipstick negative)

**Stage 4 (overt nephropathy):**

- Persistent **proteinuria** (albumin excretion > 300 mg/day, dipstick positive)
- **Hypertension** is present in most patients
- Histology shows diffuse **glomerulosclerosis** and focal glomerulosclerosis **(Kimmelstiel-Wilson nodules)**

**Stage 5:**

- **ESRD**, GFR typically < 10ml/min
- Renal replacement therapy needed

**N.B:**

- For the purposes of the MRCP, increase in the glomerular filtration rate (GFR) is most characteristic of stage 1 diabetic nephropathy. It is however known that elevation of the GFR usually persists into stage 2.
- The timeline given here is for type 1 diabetics. Patients with type 2 diabetes mellitus **(T2DM) progress through similar stages** but in a different timescale - **some T2DM patients may progress quickly to the later stages.**
- **Diabetic nephropathy** has **greater incidence** in **type 1** DM than type 2.
- The **majority** of patients with **diabetic nephropathy** **have type 2 diabetes,** however this is due to **higher prevalence of type 2,** rather than higher incidence of nephropathy (as incidence is in fact higher in T 1 DM).
- Nephropathy itself is signalled by the excretion of trace amounts of protein in the urine microalbuminuria.
- The progression of the disease may be attenuated by stringent BP control with ACEIs and strict glycaemic control.
- **In type 1 diabetes** the **chance** of progressing to **ESRD** would be approximately **50%** but in **type 2 diabetics** with diabetic nephropathy it is **15%** be expected to progress to ESRD.

A recent case series demonstrated that there is **worsening** of **renal function** in up to **45%** of patients who **get pregnant with pre-existing diabetic nephropathy**.

Any diabetic female with proven diabetic nephropathy and get pregnant, she has a **45% chance of worsening renal function**.

**Recommendations are taken from the NICE AND KDIGO guidelines on the management of chronic kidney disease 2021 and 2020** which state that when **initiating ACEIs therapy a 25% reduction in the eGFR** or **30% increase in the serum creatinine** is tolerable and should **not** lead to changes in dosing.

ACE inhibitors should also be **stopped** or **dose adjusted if** is there is a rise in the serum potassium level to greater than **6** mmol/l.

ARBs produce the same effects as ACEIs in terms of reduction in GFR and rise in creatinine and there is **no benefit** in changing from one to the other should the other class of drug impair renal function sufficiently that it has to be stopped.

Unfortunately, a progressive increase in serum creatinine is not unusual in the treatment of diabetic nephropathy. It is likely that the increase in creatinine seen is due to **progression of this patient's intrinsic diabetic renal disease** rather than to any other pathology such as renal artery disease upon which ACEI may have an impact.
As such the recommendation is to **continue the ACEI (Ramipril at maximal tolerated dose 10 mg daily),** as it is likely still to be having an effect in slowing progression.

**According to the latest guideline:**

All patients with CKD AND T2DM up to GFR of 30ml/min should receive SGLT2 inhibitors AND metformin. SGLT2 inhibitors improve kidney function by reducing hyperfiltration and reducing renal inflammatory, and fibrotic response to hyperglycemia.
This must be the first line of treatment to improve the cardiac function and limit deterioration of kidney function.
All patients must receive tight blood pressure control, blood sugar near normal, exercise, smoking cessation and blood lipids near normal.
Some of them might need antiplatelets.

## Screening:

**For T1DM:** after 5 years of diagnosis if below 12 years old or immediately annually if above 12 years old.
**For T2DM:** immediately after the diagnosis, annually or more frequent according to the initial investigations.

## Indications of renal biopsy in diabetic nephropathy:

**According to Mazzucoo et al,**

- having signs of another systemic disease.
- Onset of proteinuria less than 5 years after the diagnosis of T1DM.
- Absence of retinopathy in type one DM.
- Rapid deterioration of kidney function or sudden increase of proteinuria.
- Presence of haematuria, red cell or white blood cells in urine,or casts .

**Current treatment guidelines:** Tight glycaemic control, ACEi or ARABS, sodium restriction,and blood pressure control.

# Hematuria

The management of patients with hematuria is often difficult due to the absence of widely followed guidelines.

It is sometimes unclear whether patients are best managed in primary care, by urologists or by nephrologists.

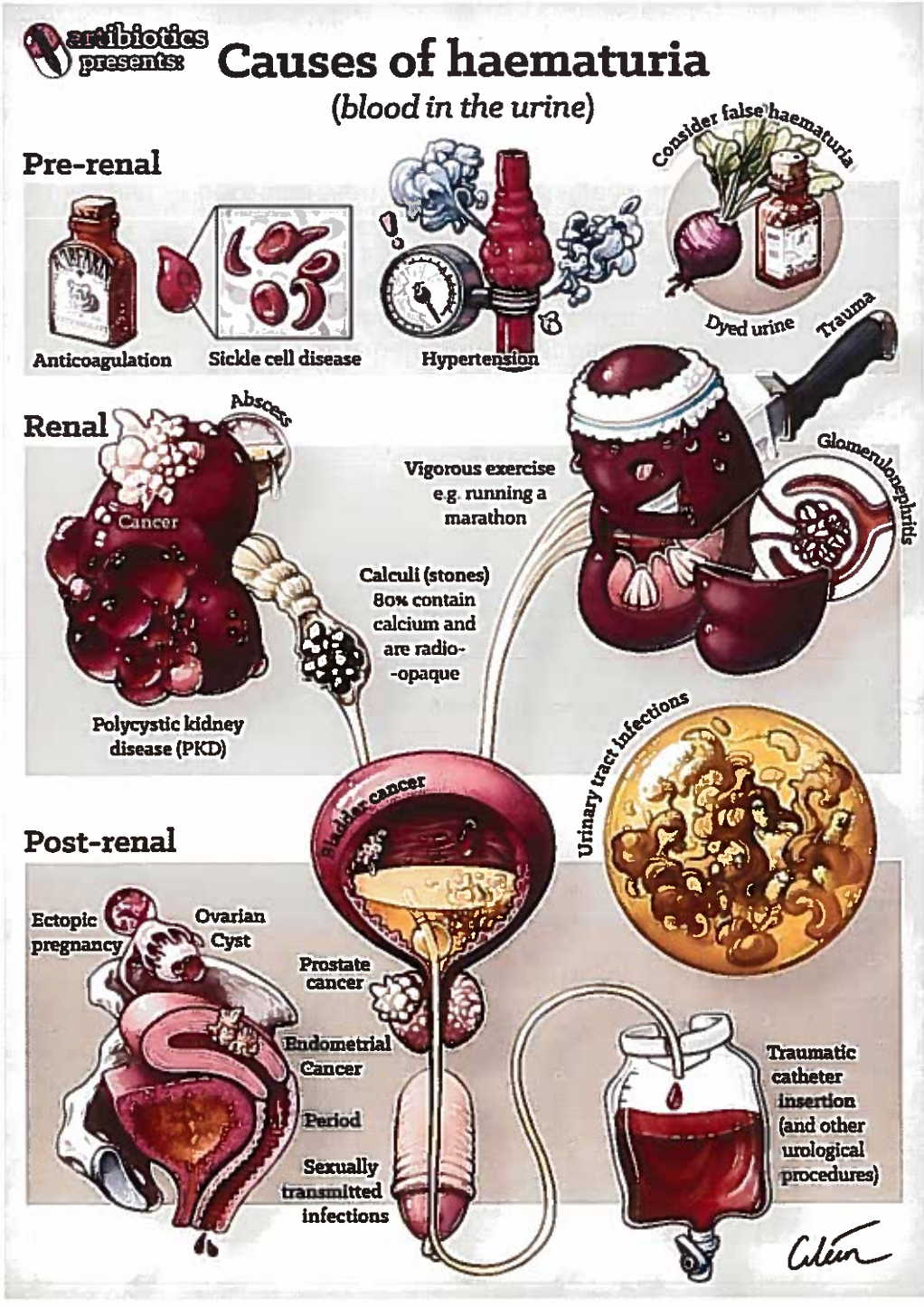
The terminology surrounding hematuria is changing. **Microscopic** or dipstick positive hematuria is increasingly termed **non-visible** hematuria whilst **macroscopic** hematuria is termed **visible** hematuria.

### Causes of transient or spurious non-visible hematuria:

- UTI
- Menstruation
- Vigorous **exercise**
- Sexual intercourse

### Causes of persistent non-visible hematuria:

- Cancer (bladder, renal, prostate)
- Stones
- Benign prostatic hyperplasia
- Prostatitis
- Urethritis e.g., *Chlamydia*
- Renal causes: IgA nephropathy, thin basement membrane disease


antibiotics presents:
Causes of haematuria
(blood in the urine)
Pre-renal
Anticoagulation
Sickle cell disease
Hypertension
Consider false haematuria
Dyed urine
Trauma
Renal
Abscess
Cancer
Polycystic kidney disease (PKD)
Vigorous exercise e.g. running a marathon
Calculi (stones) 80% contain calcium and are radio--opaque
Glomerulonephritis
Urinary tract infections
Post-renal
Bladder cancer
Ectopic pregnancy
Ovarian Cyst
Prostate cancer
Endometrial Cancer
Period
Sexually transmitted infections
Traumatic catheter insertion (and other urological procedures)

**Management**: Current evidence does not support screening for hematuria.

The incidence of non-visible haematuria is similar in patients taking aspirin/warfarin to the general population hence these patients should also be investigated as normal.

## Testing:

- **Urine dipstick** is the test of choice for detecting hematuria
- persistent non-visible hematuria is often defined as blood being present in 2 out of 3 samples tested 2-3 weeks apart
- renal function, albumin:creatinine (ACR) or protein:creatinine ratio (PCR) and blood pressure should also be checked
- Urine microscopy may be used but time to analysis significantly affects the number of red blood cells detected

### NICE urgent cancer referral guidelines:

Urgent referral (i.e., within 2 weeks)

### Aged >= 45 years AND:

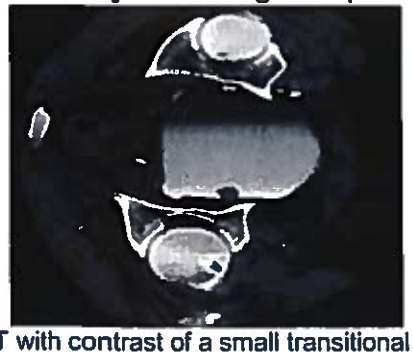
- unexplained visible hematuria without urinary tract infection, or
- visible hematuria that persists or recurs after successful treatment of urinary tract infection.

  Aged >= 60 years AND have unexplained **nonvisible hematuria** **and** either **dysuria** **or** a **raised white cell count on a blood test.**

### Non-urgent referral

Aged >= 60 years with recurrent or persistent unexplained urinary tract infection, Since the investigation (or not) of non-visible hematuria is such as a common dilemma a number of guidelines have been published. They generally agree with NICE guidance, of note:

- patients under the age of 40 years with normal renal function, no proteinuria and who are normotensive do not need to be referred and may be managed in primary care.



CT with contrast of a small transitional cell carcinoma of the bladder that was barely visible until the patient was scanned on side. A small bladder diverticulum is visible as well.

CT with contrast reveals a bladder cancer in a 68-year-old man with hematuria

# Renal stones

**General Risk factors:**

- Dehydration
- Hyperparathyroidism, hypercalcemia, Hypercalciuria
- **Cystinuria (NOT CYSTINOSIS)**
- High dietary oxalate
- Renal tubular acidosis
- Medullary sponge kidney, polycystic kidney disease
- Beryllium or cadmium exposure

**Risk factors for Urate stones:**

- Gout
- **ileostomy**: loss of bicarbonate and fluid results in acidic urine, causing the precipitation of uric acid

**Drug causes:**

- Drugs that promote **calcium** stones: **loop** diuretics, **steroids, acetazolamide, theophylline**
- Thiazides can prevent calcium stones (increase distal tubular calcium resorption)

Red blood cells (RBC s) seen in the urine of a woman passing a kidney stone. Some of the RBC s are crenated and there is one epithelial cell visible

**Oxalate stones** are uncommon in dietary excess of oxalate. However enteric oxaluria may occur in a number of disorders in which malabsorption results in excessive colonic absorption of oxalate.

**These include:**

- **Coeliac** disease
- **Crohn's** disease
- Chronic pancreatitis, and

- **Short bowel syndrome** (e.g. post jejuno-colic anastomosis for Crohn's disease).

High fluid intake and calcium carbonate are mainstay of prevention.

**EX:** A 20-year-old boy is admitted with renal colic due to renal calculus.
His mother has a similar history of recurrent calculi.
The most likely explanation for recurrent renal calculi in both mother and child
**>>> Idiopathic hypercalciuria**
Idiopathic hypercalciuria has a **familial** or **sporadic** pattern.
In the **familial** pattern an **autosomal dominant** inheritance is present.
There is **normal serum Calcium**, BUT **raised urinary excretion of calcium**: increased **24 hrs urinary calcium** **18** mmol/24 hr (N: 2.5-7.5).

The type of the disease is identical in affected members of the same family and the typical presentation is of **recurrent urinary calculi.**

**Treatment:**
1) **High fluid intake** (aim for a daily UOP≥ 2000 ml),
2) Reducing his dairy dietary intake he may reduce his GIT absorption of calcium,
2) **Thiazide** diuretics reduce renal tubular calcium excretion, and therefore can prevent calcium stone formation,
3) Potassium citrate also chelates calcium and is useful in combination with thiazides in those who develop hypokalaemia on diuretics.

**Medullary sponge kidney** is a disorder which can affect part, one or both kidneys, resulting in **ectatic** and **cystic** changes of the medullary and papillary **collecting ducts.**
It is often associated with **calculi**, which can result in pyelonephritis and renal tract obstruction.
Medullary sponge kidney is typically **not inherited** but **is a congenital condition**
The etiology is **uncertain**, but it is thought to be a developmental abnormality, possibly resulting from tubular or collecting duct obstruction at any early age.

The majority of cases are **sporadic**, although a rare **autosomal dominant** familial form exists with onset in adulthood, and a juvenile autosomal recessive form is also recognized.

Recent research has identified a possible defect in the development of the proton pump mechanism in the kidney.

## Renal stones: imaging

The table below summarizes the appearance of different types of renal stone on x-ray.

| Type | Frequency | Radiograph appearance |
|---|---|---|
| **Calcium oxalate** | **40%** | Opaque |
| Mixed calcium oxalate/phosphate stones | 25% | Opaque |
| Triple phosphate stones* | 10% | Opaque |
| Calcium phosphate | 10% | Opaque |
| **Urate** stones | 5-10% | Radio-**lucent** |
| **Cystine** stones | 1% | Semi-opaque, 'ground-glass' appearance |
| Xanthine stones | <1% | Radio-**lucent** |

Non-contrast C T of the abdomen and pelvis of a woman showing several of the stones

**NB:** The most common composition of renal stones in the general population is **Calcium oxalate**, followed by **calcium phosphate.** Together these make up a significant majority of stones.

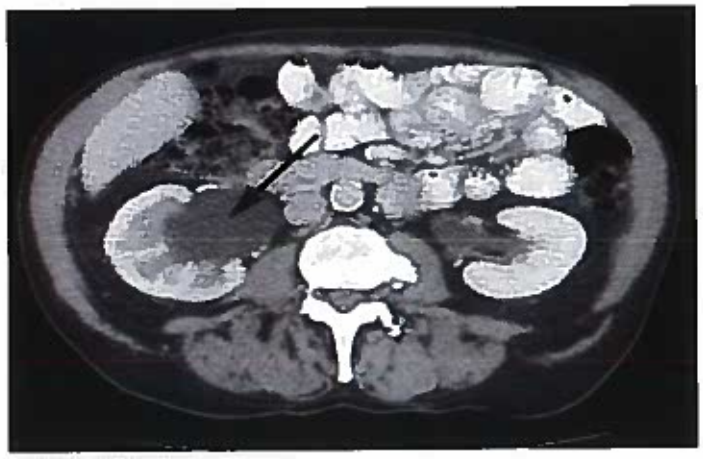
**NB:** Calcium phosphate stones are seen in renal tubular acidosis (RTA).

## Stag-horn calculi

- Composed of **Struvite** (**ammonium magnesium phosphate**, triple phosphate)
- Form in **alkaline** urine (classically produced by **urea splitting organisms**, **ammonia** producing bacteria such as **Ureaplasma urealyticum** , **Klebsiella** and **Proteus**)
- It involves the renal pelvis and extends into at least 2 calyces.
- **Treatment:** Antibiotics, Urease inhibitors, urine acidification with Vit C.

Bilateral staghorn calculi

An unenhanced C T performed on a 49-year-old woman with known renal stones reveals a large left staghorn calculus. The striated appearance of the left renal cortex is seen in obstruction, infection, and ischemia.



Right hydronephrosis duo to obstruction by stone.

Intravenous urogram showing left hydronephrosis and hydroureter

**Renal stones on x-ray**

- **Cystine** stones: semi-opaque
- **Urate + xanthine** stones: radio-lucent

# Renal stones: management

## Acute management of renal colic

### Medication:

- The British Association of Urological Surgeons **(BAUS)** recommend **diclofenac** (intramuscular/oral) as the analgesia of choice for renal colic.
- BAUS also endorse the widespread use of **alpha-adrenergic blockers** to **aid ureteric stone passage.**

Diclofenac use is now less common following the MHRA warnings about cardiovascular risk. It is therefore likely the guidelines will change soon to an alternative NSAID such as naproxen.

### Imaging:

- Patients presenting to the Emergency Department usually have a KUB x-ray (shows 60% of stones)
- The imaging of choice is a non-contrast CT (**NCCT**). **99%** of stones are identifiable on NCCT. Many GPs now have direct access to NCCT

**Stones < 5 mm will usually pass spontaneously.**
Lithotripsy and nephrolithotomy may be for severe cases.

### Prevention of renal stones:

**Calcium stones** may be due to hypercalciuria, which is found in up to 5-10% of the general population.

- High fluid intake
- Low animal protein, low salt diet (a low calcium diet has not been shown to be superior to a normocalcaemic diet)
- Thiazide diuretics (increase distal tubular calcium resorption)

### Oxalate stones:

- **Cholestyramine** reduces urinary oxalate secretion
- **Pyridoxine** reduces urinary oxalate secretion

### Uric acid stones:

- Allopurinol
- Urinary alkalinization e.g. oral bicarbonate

## Cystinuria

- It is **Autosomal recessive** disorder (AR) characterized by **recurrent** renal stones in **young** ages.
- Cystinuria is the commonest inborn error of amino acid transport.
- It is due to defect in the membrane transport of Cystine, Ornithine, Lysine, and Arginine. (Mnemonic = **COLA**).
- The **glomerulus is unable to resorb** these amino acids, so **accumulation of Cystine in collecting system** and they are therefore excreted into the urine.
- **NO** functional defects within the glomeruli.
- **NO** Cystine deposits within the Cornea.
- The rBAT gene is responsible, and there are 3 forms distinguished by the pattern of tubular amino acid transport.

**Genetics:**

- Chromosome **2**: SLC3A1 gene and Chromosome **19**: SLC7A9.

**Features:**

- **Recurrent renal stones** in the form of Cystine stones (which are often **bilateral, multiple**, and can form staghorn, it is **yellow, crystalline**, (**semi-opaque** on X-ray).

**Diagnosis: stone analysis, Cyanide-nitroprusside test.**

**Management:**

- Conservative
- Good hydration (>4 litres / day)
- **D-penicillamine** as a chelation therapy.
- Urinary **alkalinization** with NaHCO3 (PH 7.5-8)
- Cystine stones are **not easily** broken by **lithotripsy**, and therefore percutaneous removal is most often used if they do develop.

The **Cystine stones** are **radio-opaque** due to the presence of **sulphur**.
On plain film, which is not used as much in the UK any more, they are **radio-lucent.**
On CT, as with almost all stones, cysteine stones are **radio-opaque**.

## Homocystinuria

- It is rare **autosomal recessive** disorder (AR) caused by **deficiency of cystathionine beta synthase**. This results in an accumulation of homocysteine which is then oxidized to homocysteine.

**Features:**

- Fine fair hair.
- Skin: **malar flush, livedo reticularis.**
- Musculoskeletal: may be **similar to Marfan's syndrome.**

- **Neurological: & Psychiatric:** (in up to 60% of cases): Pyramidal tract symptoms, learning difficulties, mentally retarded, behaviour problem, seizures.
- **Ocular:** downwards dislocation of the lens
  **(Marfan's has upward dislocation of the lens).**
- Increase risk of **arterial** and **venous thromboembolism** except coronaries, but may present with **MI**.

**Diagnosis:**

- Urinary homocystine level.
- Measuring cystathione synthase activity in liver biopsy.
- **Cyanide-nitroprusside test.** (Which is also +ve in cystinuria).

**Treatment: Vit B6, folic acid.**

**Homocystinuria** is caused by a **deficiency** of **cystathionine beta synthase**

Interestingly, patients with **Down's syndrome** have an **excess** of **cystathionine beta synthase.**

## Acid base and electrolytes

### Renal tubular acidosis (RTA)

**Anion gap**

The anion gap is calculated by:
(sodium + potassium) - (bicarbonate + chloride)
A normal anion gap is 8-14 mmol/L
It is useful to consider in patients with a metabolic acidosis:

**Causes of a normal anion gap or hyperchloraemic metabolic acidosis**

- gastrointestinal bicarbonate loss: diarrhea, ureterosigmoidostomy, fistula
- renal tubular acidosis
- drugs: e.g., acetazolamide
- ammonium chloride injection
- Addison's disease

**Causes of a raised anion gap metabolic acidosis**

- lactate: shock, hypoxia
- ketones: diabetic ketoacidosis, alcohol
- urate: renal failure
- acid poisoning: salicylates, methanol
- 5-oxoproline: chronic paracetamol use

All three types of renal tubular acidosis (RTA) are associated with **hyperchloremic metabolic acidosis (Normal anion gap).**

## Type 1 RTA (Distal):

- **Inability to generate acid urine (secrete H+)** in distal tubule
- So this results in an **inability to acidify the urine >> serum acidosis.**
- **Alkaline urine** increases the risk of **calcium deposition,** and therefore nephrocalcinosis is a feature of type 1 RTA.
- **Hypercalciuria** and **hyperphosphaturia** occur due to the release of calcium phosphate from bone in order to buffer excess H+ during acidosis, and the direct effects of acidosis on tubular reabsorption on these ions.
- Subsequent bone demineralisation results in Rickets in children and osteomalacia in adults.
- It causes **hypokalaemia** which can result in weakness.
- **Causes** include **idiopathic, RA, SLE, Sjogren's & Sickle cell disease.**
- **Complications** include **nephrocalcinosis** and **renal stones.**
- **Treatment**: **HCO3 replacement** (1-3 mmol/kg/day), however **hypokalaemia** must be **corrected before** the acidosis in order to prevent a further fall in K and the risk of cardiac arrest.

**EX**: A 35-year-old man presents with left **loin pain and haematuria**. He comments that he has had three episodes of similar symptoms in the past. Investigations (Creatinine, Na, K, Ca, VBG, CL, and UA) showed: **Low K** 2.9 mmol/L, **Hyperchloraemic metabolic acidosis** (↑ Cl, ↓ HCO3), **Urine: pH 6.5**, pus 1+, RBC 1+, Protein 1+. What is the most likely diagnosis **>>> RTA 1**

The presence of **alkaline urine of pH more than 5.5** here, with symptoms suggestive of a **renal tract stone**, means that **type 1 RTA** is the most likely diagnosis.

**EX**: female patient 25 years old known to have **SLE**, she has **acute severe loin pain** with **UTI** and Labs: **low K=3.3, metabolic acidosis, alkaline urine PH 7.4 >>> RTA type 1 secondary to lupus.**

## Type 2 RTA (proximal):

- **Usually occurs in infancy.**
- **Decreased HCO3- reabsorption in proximal tubule.**
- As the distal tubule functions normally, the **acidosis is less** severe than type 1 RTA, and they urine has a pH of less than 5.3.
- It causes **hypokalemia**
- Rather than being a solitary defect, type 2 RTA is usually associated with a more generalized dysfunction of tubular cells which manifests as

Fanconi's syndrome (phosphaturia, glycosuria, aminoaciduria, uricosuria, tubular proteinuria). Phosphate wasting results in marked bone demineralization.

- **Causes & associations** of RTA 2 include:
  - **Idiopathic**, as part of **Fanconi** syndrome,
  - **Wilson's** disease (check Kayser-Fleischer ring),
  - Hereditary fructose intolerance
  - Lowe's syndrome.
  - **Cystinosis,**
  - **Heavy metal poison**
  - Drugs: **Acetazolamide**, outdated **tetracyclines** and certain chemotherapy.
- **Complications** include **osteomalacia.**
- Nephrocalcinosis in **NOT** a feature in RTA type II.
- **Treatment:** **HCO3** replacement + **thiazide**.

**Type 3 RTA (juvenile RTA):**

- It is **combined** Proximal and distal RTA.
- Results from **inherited carbonic anhydrase II deficiency (C.A. II Def.).**
- Mutations in the gene encoding this enzyme give rise to:
  - RTA.
  - AR syndrome of **osteopetrosis**
  - **Cerebral calcification.**
  - **Mental retardation.**
- 70% of the reported cases are from the **Maghreb** region of North Africa.

**Type 4 RTA (hyperkalaemia):**

- **It causes hyperkalaemia.**
- It **is not actually a tubular disorder at all** nor does it have a clinical picture similar to the other RTAs.
- **It is associated** with normal anion gap metabolic acidosis due to **physiological ↓ in proximal tubular ammonium excretion.**
- It is associated with **hyperkalaemia** as there is a **hypo-reninemic hypo-aldosteronism**, hence **hyperkalaemia** and **hyponatraemia** is more typical.
- **Causes** include:
  1. **DM.**
  2. **Hypo-aldosteronism**

- This Hypoaldosteronism either:
  - Aldosterone **deficiency**: which is either **Primary** vs. **secondary** due to hypo-reninemic (hypo-reninemic hypo-aldosteronism).
  - Aldosterone **resistance**:
    - Drugs: Amiloride, Spironolactone, ACEI, ARBs, Heparin, NSAIDS, Trimethoprim, Pentamidine.
    - Pseudohypoaldosteronism.
    - Structural kidney disease as SLE, amyloidosis.
- **Treatment**: it depends on the underlying cause.
  - If there is aldosterone deficiency: **fludrocortisone** can be used.
  - In cases of aldosterone resistance: **dietary K restriction**, **loop diuretics** and **low dose oral NaHCO3** can be trialled.

# ACID BASE ANALYSIS

by Nick Mark MD

ONE onepagericu .com @nickmmark

Link to the most current version →

**What's the primary disturbance?**

**1. pH**

- >7.4 → alkalemia
- <7.4 → acidosis

**What's the pCO2?**

**2. $pCO_2$**

- ↑ → respiratory acidosis
- ↓ → respiratory alkalosis

*Acute or chronic?*

What is the chronicity?
Look at metabolic compensation
Acute: 10 Δ $pCO_2$ → 0.08 Δ pH
Chronic: 10 Δ $pCO_2$ → 0.03 Δ pH

↑Drive
- Airflow obstruction
  - COPD, asthma
- ↓Drive
  - Medications
  - Central
- ↑CO2 production

↑ drive
- Pain/anxiety
- Hepatic enceph
- Pregnancy
- Salicylates

**What's the bicarb?**

**3. $HCO_3^-$**

- ↑ → metabolic alkalosis
- ↓ → metabolic acidosis

Is the anion gap increased?
AG = [Na] + ([Cl] + [$HCO_3$])
Expected AG = 2.5 x Albumin
If AG > expected AG, there is an anion gap present

"BLVD PLACE"
- B - Bartter's
- L – Laxative
- V – Vomitting
- D - Diarrhea/diuretics
- P - Post-hypercapnea
- L - Licorice
- A - Alkali ingestion
- C - Contraction alkalosis
- E - Endocrine (Conn's or Cushing's)

*Is there compensation?*

If there is a metabolic acidosis or alkalosis present is there appropriate respiratory compensation?
Use one of two rules of find out:
1. Expected $pCO_2$ = 1.5 x [HCO3] + 8 ± 2 (Winter's)
2. Expected $pCO_2$ = last two digits of pH
If the measured pCO2 does not match the expected value, there is also a respiratory derangement.

non anion gap metabolic acidosis

"RAGES"
- R – RTA
- A – Ammonia, Acetazolamide, HyperAlimentation
- G – GI losses
- E – Endocrine
- S – Saline

anion gap metabolic acidosis

"GOLDMARKeT"
- G – Glycols
- O – Oxoproline
- L – Lactic acid
- D – Lactic acid
- M – Methanol
- A – Aspirin
- R – Renal fail, Rhabdo
- Ke – Ketones
- T – Toluene

Does the change in AG account for the change in $HCO_3$?
Used to determine if there is another derangement.

**4. $\frac{\Delta HCO_3}{\Delta AG}$**

*Does $\Delta HCO_3 \approx \Delta AG$?*

- ↑ΔΔ > 1.5 → superimposed metabolic alkalosis
- NO
- YES
- ↓ΔΔ < 0.8 → superimposed NAGMA → Salicylate poisoning, DKA w/ dehydration
- No other derangement

v1.0 (8/2015)

# EPIDEMIOLOGY + PATHOGENESIS

## of Metabolic Acidosis in Chronic Kidney Disease

## INTRODUCTION

### Prevalence

**Affects ~15% of all CKD patients with prevalence increasing in later stages of CKD**

### Definition

A condition in which the body has an acid content that is too high to support good health, defined as a **serum bicarbonate <22 mEq/L in a patient**

## ACID-BASE BALANCE

| Input | Output |
|---|---|
| **Acid load from diet and protein metabolism** | **Lungs ($CO_2$)**<br>**Kidneys ($NH_4^+$ and titratable acids)** |

## MECHANISM

**Kidney acid excretion is decreased in chronic kidney disease due to reduced nephron mass**

### Proximal Tubule

**~80% of filtered bicarbonate reabsorbed**

**Glutamine metabolism yields $NH_4^+$ and $HCO_3^-$**

**$NH_4^+$ enters urinary space by NHE3 (sodium-hydrogen exchanger 3) or $H^+$/ATPase (proton pump)**

### Along the Nephron

**$HPO_4^{2-}$ binds to secreted $H^+$**
**When urine pH ≤5.5, virtually all phosphate is protonated and buffers like uric acid and creatinine contribute to titratable acid excretion**

### Thick Ascending Limb

**15% of filtered bicarbonate reabsorbed**

**$NH_4^+$ enters cells by NKCC2 (Na-K-Cl cotransporter 2)**

**$NH_4^+$ enters interstitium by NHE4 (sodium-hydrogen exchanger 4) and generates interstitial $NH_4^+$ concentration gradient**

### Collecting Duct

**$NH_3$ and $H^+$ recombine to form $NH_4^+$ which is secreted into urine**

## AMMONIUM ($NH_4^+$)

**Produced mainly in proximal tubule from glutamine metabolism**

**Glutamine is mainly from diet and muscle protein degradation**

**Excreted in urine as major adaptive kidney response to acid load**

## TITRATABLE ACIDS

**Urinary buffers derived from the systemic circulation**

**The principal titratable buffer is $HPO_4^{2-}$ (90% of titratable acid excretion as $H_2PO_4^-$)**

# CONSEQUENCES (1)

## of Metabolic Acidosis in Chronic Kidney Disease

## INTRODUCTION

### Prevalence

**Affects ~15% of all CKD patients with prevalence increasing in later stages of CKD**

### Currently Undertreated

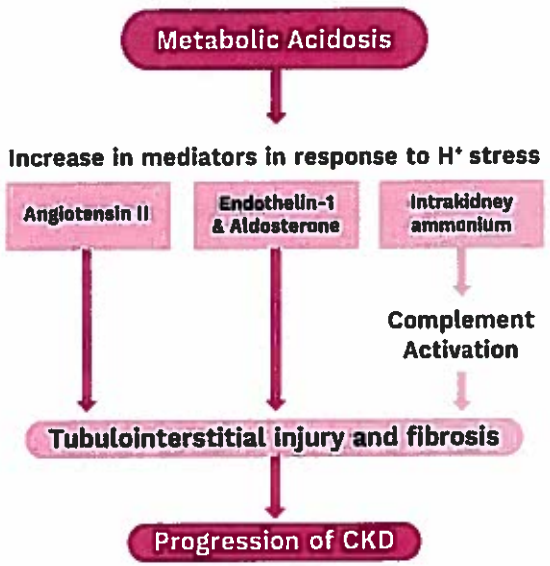
**Only 2.7% of patients with CKD and serum bicarbonate ≤22 mEq/L receive oral alkali**

### Why Should We Treat?

**Metabolic acidosis is associated with faster progression of CKD and increased mortality.**

**Multiple studies have shown that treatment can slow the decline in kidney function.**

## PROGRESSION OF CKD




### Angiotensin II

Can trigger interstitial inflammation, fibrosis, tubular atrophy, and proteinuria that progressively reduces kidney function

**Enhances ammoniagenesis and kidney production of endothelin-1 and aldosterone, therefore possibly accelerates progression of kidney dysfunction**

**This can be reduced by alkali supplementation and consumption of base-producing foods, which can then slow the rate of eGFR decline in patients with CKD**

### Endothelin-1 (ET-1) and Aldosterone

**Sustained elevated ET-1 levels are associated with increased tubulointerstitial damage, inflammation and fibrosis, leading to increased glomerular permeability and overall GFR decline**

Aldosterone generation (in response to stimulation of intrakidney renin-angiotensin-aldosterone system) **increases distal nephron acidification and causes hemodynamic and profibrotic effects that promote kidney damage**

**Alkali supplementation was shown to ameliorate kidney injury due to ET-1 and reduced kidney cortical aldosterone production (in a rat remnant kidney model)**

### Ammoniagenesis

Ammonia reacts with complement C3 to form a **convertase that activates the alternative complement pathway, increases inflammation and tubulointerstitial damage**

# CONSEQUENCES (2)

## of Metabolic Acidosis in Chronic Kidney Disease

### INTRODUCTION

#### Prevalence

**Affects ~15% of all CKD patients** with prevalence increasing in later stages of CKD

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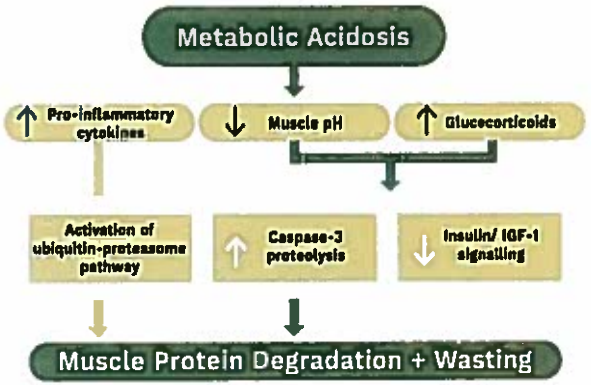
**Only 2.7%** of patients with CKD and serum bicarbonate ≤22 mEq/L receive oral alkali

#### Why Should We Treat?

Metabolic acidosis is associated with faster progression of CKD and increased mortality.

**Multiple studies have shown that treatment can slow the decline in kidney function.**

### PROTEIN CATABOLISM




**Muscle Wasting**

Characterized by **increased muscle turnover** rate and atrophy of type II muscle fibers

Associated with **increased muscle protein degradation** without a change in muscle protein synthesis

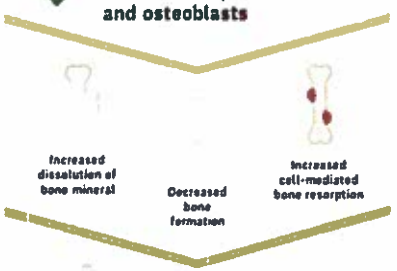
Administration of alkali supplementation to patients with CKD not yet on dialysis or those on maintenance dialysis **increased lean body mass, improved muscle strength and dietary protein intake, reduced protein catabolic rate, increased serum albumin levels, and improved physical functioning**

### BONE DISEASE

**pH of interstitial fluid of bone**

**systemic pH**

**intracellular pH of osteoclasts and osteoblasts**




**Osteomalacia**

**Osteitis fibrosa cystica**

# CONSEQUENCES (3)

## of Metabolic Acidosis in Chronic Kidney Disease

## INTRODUCTION

### Prevalence

**Affects ~15% of all CKD patients** with prevalence increasing in later stages of CKD

### Currently Undertreated

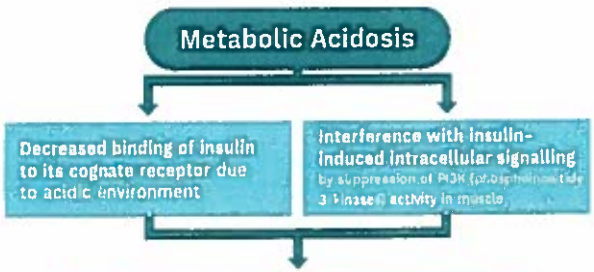
**Only 2.7%** of patients with CKD and serum bicarbonate ≤22 mEq/L receive oral alkali

### Why Should We Treat?

Metabolic acidosis is associated with faster progression of CKD and increased mortality.

**Multiple studies have shown that treatment can slow the decline in kidney function.**

## ENDOCRINE ABNORMALITIES


Metabolic Acidosis
Decreased binding of insulin to its cognate receptor due to acidic environment
Interference with insulin-induced intracellular signalling by suppression of PI3K (phosphoinositide 3-kinase) activity in muscle
Decreased Insulin Sensitivity

Insulin resistance correlated with severity of metabolic acidosis in patients with CKD without diabetes

### Insulin-like Growth Factor-1 (IGF-1)

Lower levels in metabolic acidosis

Blunted response to **administration of pharmacologic doses of growth hormone (GH)**

Correction of metabolic acidosis improved IGF-1 responsiveness to GH administration

### Thyroid Function

Induction of metabolic acidosis in humans with normal kidney function showed signs of **hypothyroidism**

Patients with CKD demonstrated **reduced plasma T3 and T4 levels with normal thyroid stimulating hormone and a blunted response to thyrotropin**

Correction of metabolic acidosis in hemodialysis patients **restored plasma T3 levels**

## COGNITION

A lower serum bicarbonate level is independently associated with lower performance in tests evaluating global cognitive / executive function

### Proposed mechanisms of acidosis-induced neuronal dysfunction include:

Inhibition of NMDA (N-methyl-D-aspartate)-activated currents by acidosis leading to overexcitation of neural networks

Acidosis induced by a Western diet (irrespective of eGFR) promoting neural excitotoxicity and subsequent cognitive impairment

# Diabetes insipidus

Diabetes insipidus (DI) is a condition characterised by either a decreased secretion of antidiuretic hormone (ADH) from the pituitary (cranial DI) or an insensitivity to antidiuretic hormone (nephrogenic DI).

## Causes of cranial DI

- idiopathic
- post head injury
- pituitary surgery
- craniopharyngiomas
- infiltrative
  - histiocytosis X
  - sarcoidosis
- DIDMOAD is the association of cranial Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy and Deafness (also known as Wolfram's syndrome)
- haemochromatosis

## Causes of nephrogenic DI

- **genetic: the more common form affects the vasopression (ADH) receptor, the less common form results from a mutation in the gene that encodes the aquaporin 2 channel**
- electrolytes: hypercalcaemia, hypokalaemia
- lithium
  - **lithium desensitizes the kidney's ability to respond to ADH in the collecting ducts**
- demeclocycline
- tubulo-interstitial disease: obstruction, sickle-cell, pyelonephritis

## Features

- polyuria
- polydipsia

## Investigation

- high plasma osmolality, low urine osmolality
- a urine osmolality of >700 mOsm/kg excludes diabetes insipidus
- water deprivation test

## Management

- nephrogenic diabetes insipidus: thiazides, low salt/protein diet

central diabetes insipidus can be treated with desmopressin

## Fanconi syndrome

Fanconi syndrome describes a generalised disorder of renal tubular transport resulting in:

- **Type 2** (**proximal**) renal tubular acidosis
- **Aminoaciduria**
- **Glycosuria**
- **Phosphaturia**
- **Osteomalacia**

### Causes:

- **Cystinosis** (most common cause in children)
- Sjogren's syndrome
- Multiple myeloma
- Nephrotic syndrome
- Wilson's disease

## Fluid therapy

The prescription of intravenous fluids is one of the most common tasks that junior doctors need to do.

### NICE guidelines recommend the following requirements for maintenance fluids:

- 25-30 ml/kg/day of water and
- approximately **1 mmol/kg/day of potassium**, sodium and chloride and
- approximately 50-100 g/day of glucose to limit starvation ketosis

**So, for a 80kg** patient, for a 24 hour period, this would translate to:

- 2 liters of water
- 80mmol potassium

### For the first 24 hours NICE recommend the following:

When prescribing for routine maintenance alone, consider using 25-30 ml/kg/day sodium chloride 0.18% in 4% glucose with 27 mmol/l potassium on day 1 (there are other regimens to achieve this).

The amount of fluid patients require obviously varies according to their recent and past medical history.

For example, a patient who is post-op and is having significant losses from drains will require more fluid whereas a patient with heart failure should be given less fluid to avoid precipitating pulmonary oedema.

The table below shows the electrolyte concentrations (in millimoles/liters) of plasma and the most commonly used fluids:

| | $Na^+$ | $Cl^-$ | $K^+$ | $HCO3^-$ | Glucose |
|---|---|---|---|---|---|
| Plasma | 135-145 | 98-105 | 3.5-5 | 22-28 | - |
| 0.9% saline | 154 | 154 | - | - | - |
| 5% glucose | - | - | - | - | 50g |
| 0.18% saline with 4% glucose | 30 | 30 | - | - | 40g |
| Hartmann's solution | 131 | 111 | 5 | 29 | - |

## Specific points

### 0.9% saline

- **if large volumes are used there is an increased risk of hyperchloremic metabolic acidosis**

### Hartmann's

- contains potassium and therefore should not be used in patients with hyperkalemia

# Hyperkalaemia

Untreated hyperkalemia may cause life-threatening arrhythmias. Precipitating factors should be addressed (e.g., acute kidney injury) and aggravating drugs stopped (e.g., ACE inhibitors). Management may be categorized by the aims of treatment

## Staging

### The European Resuscitation Council classifies hyperkalaemia as:

- mild: 5.5 - 5.9 mmol/L
- moderate: 6.0 - 6.4 mmol/L
- severe: ≥ 6.5 mmol/L

Remember that the presence of ECG changes is important in determining the management - it should be done in all patients with new hyperkalemia.

### The following changes are associated with hyperkalemia:

- peaked or 'tall-tented' T waves (occurs first)
- loss of P waves
- broad QRS complexes
- sinusoidal wave pattern

ECG showing severe hyperkalaemia: QRS widening and peaked T waves

## Management

### Principles of treatment modalities

**A-Stabilization of the cardiac membrane**

- **IV calcium gluconate**
  - does NOT lower serum potassium levels

**B-Short-term shift in potassium from extracellular (ECF) to intracellular fluid (ICF) compartment.**

- combined insulin/dextrose infusion
- nebulized salbutamol

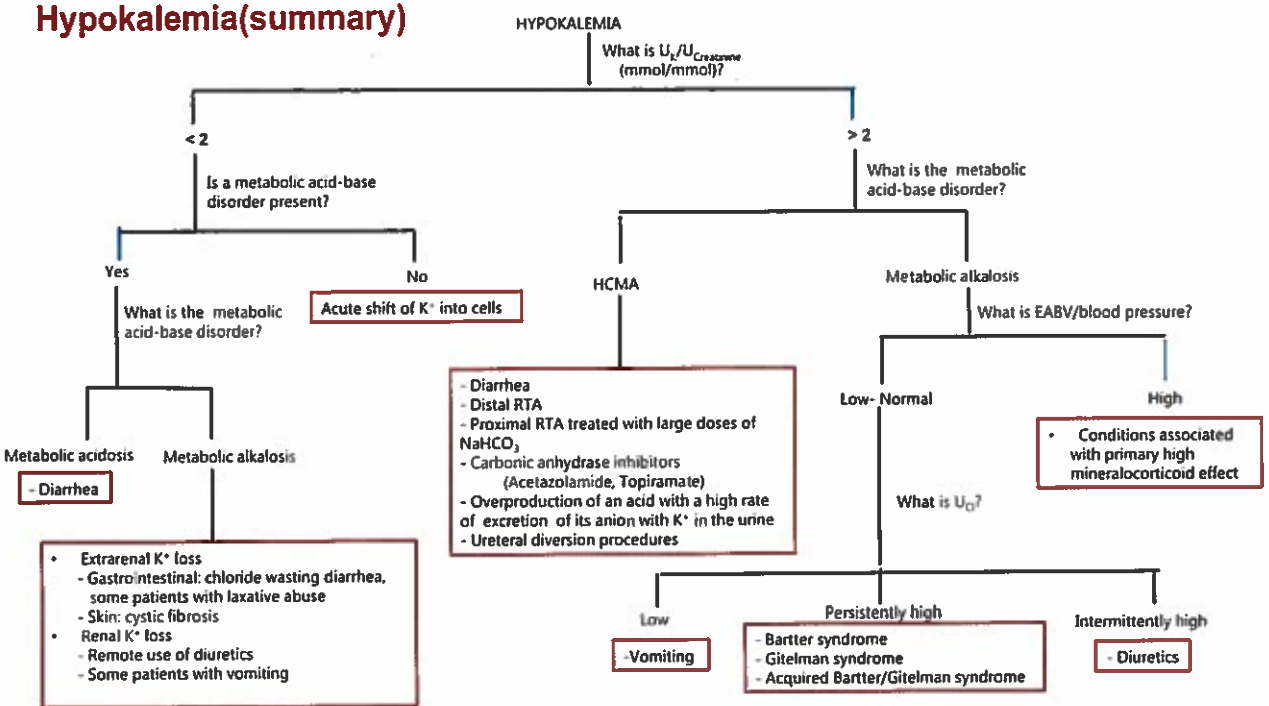
**(They Donot Have Additive Value and The Effect Is Transient)**

**C-Removal of potassium from the body.**

**NEW TREATMENT ZERCONIUM THIOSILICATE(SZ69) AND PATEROMER**

- **calcium resonium** (orally or enema) OLD TREATMENT.
  - enemas are more effective than oral as potassium is secreted by the rectum, BUT unpalatable and can cause necrotizing colitis in old people.
- **loop diuretics**
- **Dialysis**
  - hemofiltration/hemodialysis should be considered for patients with AKI with persistent hyperkaliemia

## Hypokalemia(summary)




Urine data in the clinical approach to the patients with hypokalemia. A urine potassium (UK)/urine creatinine (UCreatinine) <2 and the absence of a metabolic acid-base disorder suggest that the major cause of hypokalemia is an acute intracellular shift of Kþ. The UK/UCreatinine may be <2 in some patients with renal Kþ loss (e.g., some patients with vomiting) and >2 in some patients with extrarenal Kþ loss (some patients with diarrhea). The causes for renal Kþ loss can be differentiated by the associated metabolic-acid base disorder. In patients with metabolic alkalosis, further differential diagnosis is based on assessment of the effective arterial blood volume (EABV) and the blood pressure. In the group with low/normal EABV and blood pressure, measurement of chloride concentration in the urine (UCl) provides useful clues to determine the cause of the renal Kþ loss. Conditions associated with primary increased mineralocorticoid effect include primary hyperreninemic hyperaldosteronism (e.g., renal artery stenosis, renin-secreting tumor), primary hyperaldosteronism (e.g., adrenal adenoma, bilateral adrenal hyperplasia, glucocorticoidremediable hyperaldosteronism), conditions in which cortisol acts as a mineralocorticoid (e.g., apparent mineralocorticoid excess syndrome, ingestion of compounds containing glycyrrhizic acid which inhibits 11 b hydroxysteroid dehydrogenase-2, adrenocorticotropic hormone-producing tumor), and constitutively active epithelial sodium channel (e.g., Liddle syndrome). RTA, renal tubular acidosis; HCMA, hyperchloremic metabolic acidosis; NaHCO3, sodium bicarbonate.

# Lower urinary tract symptoms in men

Lower urinary tract symptoms (LUTS) in men are very common and are present in the majority of men aged > 50 years.
They are most commonly secondary to benign prostatic hyperplasia but other causes should be considered including prostate cancer.
**It is useful to classify the symptoms into 3 broad groups.**

| Voiding | Storage | Post-micturition |
|---|---|---|
| Hesitancy<br>Poor or intermittent stream<br>Straining<br>Incomplete emptying<br>Terminal dribbling | Urgency<br>Frequency<br>Nocturia<br>Urinary incontinence | Post-micturition dribbling<br>Sensation of incomplete emptying |

## Examination

- urinalysis: exclude infection, check for hematuria
- digital rectal examination: size and consistency of prostate
- a PSA test may be indicated, but the patient should be properly counselled first

**It is useful to get the patient to complete the following to guide management:**

- urinary frequency-volume chart: distinguish between urinary frequency, polyuria, nocturia, and nocturnal polyuria.
- **International Prostate Symptom Score (IPSS):** assess the impact on the patient's life. This classifies the symptoms as mild, moderate or severe

## Management

### Predominately voiding symptoms

- conservative measures include: pelvic floor muscle training, bladder training, prudent fluid intake and containment products
- if 'moderate' or 'severe' symptoms offer an alpha-blocker
- if the prostate is enlarged and the patient is 'considered at high risk of progression' then a 5-alpha reductase inhibitor should be offered
- if the patient has an enlarged prostate and 'moderate' or 'severe' symptoms offer both an alpha-blocker and 5-alpha reductase inhibitor
- if there are mixed symptoms of voiding and storage not responding to an alpha blocker then a antimuscarinic (anticholinergic) drug may be added

### Predominately overactive bladder

- conservative measures include moderating fluid intake
- bladder retraining should be offered

- antimuscarinic drugs should be offered if symptoms persist. NICE recommend oxybutynin (immediate release), tolterodine (immediate release), or darifenacin (once daily preparation)
- mirabegron may be considered if first-line drugs fail

**Nocturia**

- advise about moderating fluid intake at night
- furosemide 40mg in late afternoon may be considered
- desmopressin may also be helpful

## Urinary incontinence (UI)

Urinary incontinence (UI) is a common problem, affecting around 4-5% of the population. It is more common in elderly females.

### Causes:

- **Overactive bladder (OAB)/urge incontinence**: due to detrusor over activity.
- **Stress** incontinence: leaking small amounts when coughing or laughing.
- **Mixed** incontinence: both urge and stress.
- **Overflow** incontinence: due to bladder outlet obstruction, e.g., due to prostate enlargement.

### Initial investigation:

- Bladder diaries should be completed for a minimum of 3 days
- Vaginal examination to exclude cystocele
- Urine dipstick and culture

**Management** depends on whether urge or stress UI is the predominant picture.

If urge incontinence is predominant:

- **Bladder retraining** is the initial intervention of choice (lasts for a minimum of 6 weeks, the idea is to gradually increase the intervals between voiding).
- Bladder stabilizing drugs: **Antimuscarinic** is first-line EX:
  - **Oxybutynin** (Uripan ®),
  - **Tolterodine** (Detrol®) and
  - **Solifenacin** (Vesicare ®).
- Surgical management: e.g., sacral nerve stimulation

**If stress incontinence is predominant:**

- Pelvic floor muscle training (for a minimum of 3 months).
- Surgical procedures: e.g. retropubic mid-urethral tape procedures.

**N.B:** Examples of **muscarinic antagonists** used in different conditions include: ipratropium (chronic obstructive pulmonary disease) and procyclidine (Parkinson's disease).

## Urinary tract infection in adults: management

### Lower urinary tract infections in non-pregnant women:

- Local antibiotic guidelines should be followed if available.
- SIGN guidelines recommend **trimethoprim** or **nitrofurantoin** for **3 days.**

**Pregnant women with symptomatic bacteriuria** should be treated with an antibiotic for 7 days. A urine culture should be sent.

### For asymptomatic pregnant women:

- A urine culture should be performed routinely at the first antenatal visit.
- If positive, a second urine culture should be sent to confirm the presence of bacteriuria.
- **SIGN recommend to treat asymptomatic bacteriuria detected during pregnancy with an antibiotic.**
- A 7day course of antibiotics should be given
- A further urine culture should be sent following completion of treatment as a test of cure.
- Nitrofurantoin should be avoided near term.

For patients with **sign of acute pyelonephritis** hospital admission should be considered:

- Local antibiotic guidelines should be followed if available.
- The BNF currently recommends a broad-spectrum cephalosporin or a quinolone for 10-14 days.

A 30-year-old woman who is 34 weeks pregnant presents with dysuria and urinary frequency. A urine dipstick is positive for nitrites and leucocytes. The most suitable antibiotic to use >> **Amoxicillin** or **Cephalexin (Keflex®)**.

# Chronic pyelonephritis

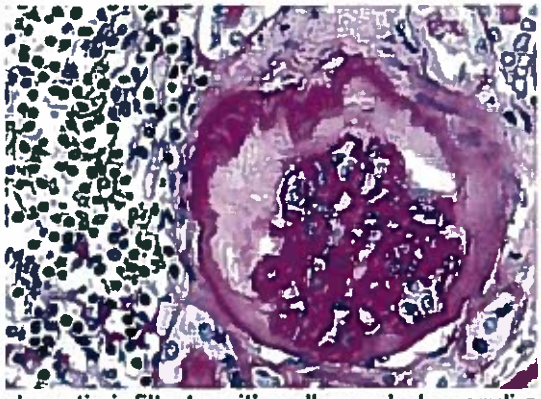
Chronic pyelonephritis is a form of chronic kidney disease caused by recurrent infections. This results in scarring of the renal parenchyma and impaired function. Chronic pyelonephritis accounts for around 15% of end-stage renal disease.

## Predisposing factors

- **vesicoureteral reflux in children**
- obstruction e.g. **recurrent renal stones**

## Key exam features

- blunted calyx
- **corticomedullary scarring with atrophy of tubules**
- eosinophilic casts in the tubules



Lymphocytic infiltrate with collapsed glomeruli and thickened Bowman's capsule.

# Xanthogranulomatous pyelonephritis

Xanthogranulomatous pyelonephritis is a rare chronic granulomatous disease resulting in a non-functioning kidney.
Chronic/subacute infection by organisms such as ***Proteus mirabilis*** predispose to renal stones including staghorn calculi. Foamy (lipid laden) macrophages are typically seen.

# Vesicoureteric reflux

Vesicoureteric reflux (VUR) is the abnormal backflow of urine from the bladder into the ureter and kidney.
It is a relatively common abnormality of the urinary tract in children and predisposes to urinary tract infection (UTI), being found in around 30% of children who present with a UTI.
As around 35% of children develop renal scarring it is important to investigate for VUR in children following a UTI

## Pathophysiology of VUR

- ureters are displaced laterally, entering the bladder in a more perpendicular fashion than at an angle
- therefore shortened intramural course of the ureter
- vesicoureteric junction cannot, therefore, function adequately

## Possible presentations

- antenatal period: hydronephrosis on ultrasound
- recurrent childhood urinary tract infections
- reflux nephropathy
    - term used to describe chronic pyelonephritis secondary to VUR
    - commonest cause of chronic pyelonephritis
    - renal scar may produce increased quantities of renin causing hypertension

## Investigation

- VUR is normally diagnosed following a **micturating cystourethrogram**
- a DMSA scan may also be performed to look for renal scarring

The table below summarises the grading of VUR

| Grade | |
|---|---|
| I | Reflux into the ureter only, no dilatation |
| II | Reflux into the renal pelvis on micturition, no dilatation |
| III | Mild/moderate dilatation of the ureter, renal pelvis and calyces |
| IV | Dilation of the renal pelvis and calyces with moderate ureteral tortuosity |
| V | Gross dilatation of the ureter, pelvis and calyces with ureteral tortuosity |

## Sterile pyuria

### Causes:

- **Partially** treated UTI
- Urethritis and sexually transmitted diseases **(STD)** e.g. ***Chlamydia***
- Renal or genitourinary **TB**
- Acute glomerulonephritis
- Tubulo-interstitial diseases
- Renal **stones**
- **Cancer:** Bladder/renal cell carcinoma in old ages
- Adult **polycystic** kidney disease
- **Analgesic** nephropathy
- **Appendicitis**

**EX: Old male** with **long history** of **loin pain, fevers** and occasional **rigors** with **increase urine pus** and **RBCs** with **sterile pyuria >>>? RCC >>> US. Ultrasound scan** of the renal tract would be the **first** investigation of choice, as it is able to pick up **95% of renal cell carcinomas (RCC) greater than 1 cm** in diameter. It would also exclude infective or inflammatory collections within the renal tract.

**EX: Old** Asian man 65 years old with **weight loss, sterile pyuria, high ESR >>> Renal tract tuberculosis.**
Genitourinary TB develops in approximately **5%** of cases of pulmonary TB and is usually due to **haematogenous** spread to the renal cortex during the primary phase of infection.
The cortical lesion my then ulcerate into the pelvis, ultimately involving the bladder, seminal vesicles and prostate.
**Diagnosis** is by several early morning urine samples for mycobacterial cultures.
**Treatment** is the same as for pulmonary TB.

## Papillary necrosis

### Causes

- chronic analgesia use
- sickle cell disease
- TB
- acute pyelonephritis
- diabetes mellitus

**Features**: fever, loin pain, hematuria

**IVU - papillary necrosis with renal scarring - 'cup & spill'**

### Benign Prostate Hyperplasia (PBH)

**Risk factors:**

- Age: around **50%** of **50** year old men will have evidence of BPH and 30% will have symptoms and around **80%** of **80** year old men have evidence of BPH.
- Ethnicity: **Black** > White > Asian

BPH typically presents with lower urinary tract symptoms **(LUTS)** such as:

- Voiding symptoms **(obstructive):** weak or intermittent urinary flow, straining, hesitancy, terminal dribbling and incomplete emptying.
- Storage symptoms **(irritative):** urgency, frequency, incontinence and nocturia.
- **Post-micturition**: dribbling
- **Complications**: UTI, retention, obstructive uropathy

### Management options:

- Watchful waiting
- Medications: **α-1 antagonists**, **5-α reductase inhibitors**. The use of **combination** therapy was supported by the medical therapy of prostatic symptoms (MTOPS) trial.
- Surgery: Transurethral resection of prostate (TURP).

**α-1 antagonists (Ex. Tamsulin, Alfuzocin):**

- ↓ Smooth muscle tone (prostate and bladder).
- Considered **first** line, improve symptoms in **around 70%** of men.
- Adverse effect: dizziness, postural hypotension, dry mouth, depression.

**5-α reductase inhibitors (EX. Finasteride):**

- **Block** the **conversion** of **testosterone** to **dihydrotestosterone** (**DHT**), which induce BPH.
- Indications: -1-BPH and -2-Male pattern baldness.
- Unlike the α-1 antagonists causes a reduction in prostate volume and hence may slow the disease progression.
- This however takes time and symptoms may not improve for **6 months**.
- They may also ↓ **PSA** concentrations by up to 50%.
- Adverse effect (1%): insomnia, depression, **erectile dysfunction (impotence), ↓libido, ejaculation** problems, **gynaecomastia**, breast tenderness.

## Scrotal problems

**Epididymal cysts**

Epididymal cysts are the most common cause of scrotal swellings seen in primary care.

### Features

- separate from the body of the testicle
- found posterior to the testicle

### Associated conditions

- polycystic kidney disease
- cystic fibrosis
- von Hippel-Lindau syndrome

**Diagnosis may be confirmed by ultrasound.**

**Management** is usually supportive but surgical removal or sclerotherapy may be attempted for larger or symptomatic cysts.

### Hydrocele

A hydrocele describes the accumulation of fluid within the tunica vaginalis. They can be divided into communicating and non-communicating:

- communicating: caused by patency of the processus vaginalis allowing peritoneal fluid to drain down into the scrotum. Communicating

hydroceles are common in newborn males (clinically apparent in 5-10%) and usually resolve within the first few months of life
- non-communicating: caused by excessive fluid production within the tunica vaginalis

**Hydroceles may develop secondary to:**
- epididymo-orchitis
- testicular torsion
- testicular tumours

**Features**
- soft, non-tender swelling of the hemi-scrotum. Usually anterior to and below the testicle
- the swelling is confined to the scrotum, you can get 'above' the mass on examination
- transilluminates with a pen torch
- the testis may be difficult to palpate if the hydrocele is large

**Diagnosis** may be clinical but ultrasound is required if there is any doubt about the diagnosis or if the underlying testis cannot be palpated.

**Management**
- infantile hydroceles are generally repaired if they do not resolve spontaneously by the age of 1-2 years
- in adults a conservative approach may be taken depending on the severity of the presentation. Further investigation (e.g. ultrasound) is usually warranted however to exclude any underlying cause such as a tumour

## Varicocele

A varicocele is an abnormal enlargement of the testicular veins. They are usually asymptomatic but may be important as they are associated with infertility.

Varicoceles are much more common on the left side (> 80%). Features:
- classically described as a 'bag of worms'
- subfertility

**Diagnosis**
- ultrasound with Doppler studies

**Management**
- usually conservative
- occasionally surgery is required if the patient is troubled by pain. There is ongoing debate regarding the effectiveness of surgery to treat infertility

# Prostate cancer

**Risk factors:**

- Age (70% of men > 80 years have evidence of it on autopsy).
- Race: African-Americans
- Family Hx
- ↑ Fat in diet
- **BPH is not a risk factor**

## Management:

### 1) Localized prostate cancer (T1/T2):

Treatment depends on life expectancy and patient choice. Options include:

- Conservative: active monitoring & watchful waiting
- Radical prostatectomy
- Radiotherapy: external beam and brachytherapy

### 2) Localized advanced prostate cancer (T3/T4):

Options include:

- Hormonal therapy: see below
- Radical prostatectomy
- Radiotherapy: external beam and brachytherapy

### 3) Metastatic (Disseminated) prostate cancer disease:

- Synthetic GnRH agonist:
  - EX. **Goserelin (Zoladex):** it provide negative feedback to the anterior pituitary.
  - **Cover initially with anti-androgen** to prevent rise in testosterone.
- Anti-androgen:
  - **Cyproterone acetate**: prevent DHT binding to intracytoplasmic protein complexes.
- Orchidectomy.

**N.B:** Anti-androgen treatment such as Cyproterone acetate should be co-prescribed when starting Gonadorelin analogues due to the risk of tumour flare.

This phenomenon is secondary to initial stimulation of luteinising hormone release by the pituitary gland resulting in increased testosterone levels.

The BNF advises **starting Cyproterone acetate 3 days before the Gonadorelin analogue**

## Bladder cancer

It is a common urological cancer with most cases being **transitional cell carcinoma**.

It has **male**: female ratio= 3:1 with **women generally having a worse prognosis** than men.

The most classical presentation is with **total, gross, painless haematuria**.

**Associated risk factors:**

- **Smoking**
- **Occupational**: **aniline dyes** used in printing and textile industry, rubber manufacture.
- **Aromatic amines**
- Prior pelvic radiotherapy.
- Exposure to a urinary metabolite of cyclophosphamide (Endoxan®).
- Schistosomiasis (S.haematobium).
- Mutations on 17p13.1, the gene coding for p53, mutations of which are associated with high grade bladder cancer.
- Mutation on 9p15 and 9p16, another tumour suppressor gene associated with low grade and superficial tumours.

**N.B:** There is **NO** significant correlation between bladder cancer and coffee, alcohol consumption, artificial sweetener intake or aspirin ingestion, despite a number of stories in the media suggesting a link.

**NB: Old** patient with frank **macroscopic hematuria >>> Cystoscopy** to exclude bladder cancer is the **first** investigation **even** with normal US

## Testicular cancer

Testicular cancer is the most common malignancy in men aged 20-30 years. Around 95% of cases of testicular cancer are germ-cell tumours. Germ cell tumors may essentially be divided into:

- seminomas
- non-seminomas: including embryonal, yolk sac, teratoma and choriocarcinoma

Non-germ cell tumors include Leydig cell tumors and sarcomas.

The peak incidence for teratomas is 25 years and seminomas is 35 years.
Risk factors include:

- infertility (increases risk by a factor of 3)
- cryptorchidism
- family history
- Klinefelter's syndrome
- mumps orchitis

## Features

- a painless lump is the most common presenting symptom
- pain may also be present in a minority of men
- hydrocele
- gynaecomastia
  - this occurs due to an increased oestrogen:androgen ratio
  - germ-cell tumours → hCG → Leydig cell dysfunction → increases in both oestradiol and testosterone production, but rise in oestradiol is relatively greater than testosterone
  - leydig cell tumours → directly secrete more oestradiol and convert additional androgen precursors to oestrogens

## Tumor markers

- germ cell tumours
  - seminomas: **seminomas: hCG may be elevated in around 20%**
  - non-seminomas: **AFP and/or beta-hCG are elevated in 80-85%**
  - LDH is elevated in around 40% of germ cell tumours

**Diagnosis:** ultrasound is first-line

## Management

- treatment depends on whether the tumour is a seminoma or a non-seminoma
- orchidectomy
- chemotherapy and radiotherapy may be given depending on staging and tumour type

## Prognosis is generally excellent

- 5 year survival for seminomas is around 95% if Stage I
- 5 year survival for teratomas is around 85% if Stage I

# Renal cell cancer (RCC) (Hypernephroma)

Renal cell cancer is also known as hypernephroma and accounts for 85% of primary renal neoplasms.

It arises from **proximal renal tubular epithelium.**

## Associations:

- More common in middle-aged men
- Smoking
- Von Hippel-Lindau syndrome
- Tuberous sclerosis
- Autosomal dominant polycystic kidney disease: incidence of renal cell cancer is only slightly increased.

## Features:

- Classical **triad**: **haematuria**, loin **pain**, abdominal **mass**, unfortunately this triad is **only** seen in **10%** of the patients diagnosed with RCC.
- Pyrexia of unknown origin.
- Left varicocele (due to occlusion of left testicular vein secondary to tumour invasion of the renal vein).
- Endocrine effects: may secrete **erythropoietin** (polycythaemia) with ↑Hb in 5%, **parathyroid** hormone (hypercalcaemia), **renin** with HTN in 30%, **ACTH.**
- 25% have metastases at presentation.
- 5-year survival rate is 60-70% in tumours confined to the kidney, dropping to 5% in those with metastases.

| T category | Criteria |
|---|---|
| **T1** | Tumour ≤ 7 cm and confined to the kidney |
| **T2** | Tumour > 7 cm and confined to the kidney |
| **T3** | Tumour extends into major veins or perinephric tissues, but not into the ipsilateral adrenal gland and not beyond Gerota's fascia |
| **T4** | Tumor invades beyond Gerota's fascia (including contiguous extension into the ipsilateral adrenal gland) |

Renal cell carcinoma. C T shows solid mass in the left kidney (*arrow*).

## Complications:

- **Polycythaemia** (due to erythropoietin secretion).
- **Canon ball metastasis**
- **Hypertension**
- **Hypercalcaemia.**

## Management:

- **Radical nephrectomy** for confined disease, unless bilateral tumours or poor renal function.
- Immunotherapy with Alpha-interferon and interleukin-2 have been used to reduce tumour size and also treat patients with metastases.
- Receptor tyrosine kinase inhibitors (e.g. sorafenib, sunitinib) have been shown to have superior efficacy compared to immunotherapy.
- Radiotherapy and chemotherapy have no proven benefit in RCC.
- **Metastatic** renal cell carcinoma:
  - **Nephrectomy** (as it may shrink the metastatic deposits) **and small molecule kinase inhibitor, or**
  - **Radiotherapy** (if not fit surgically).

*incidence of renal cell cancer is only **slightly increased** in patients with autosomal dominant polycystic kidney disease

**EX:** 60 years old male with RCC with a solitary brain metastasis >>>
Treatment: Nephrectomy and small molecule kinase inhibitor.

**Xanthogranulomatous pyelonephritis:**
It can be **difficult to** distinguish from RCC.
It typically presents with symptoms of fever, **weight loss** and **loin pain.**
It is more common in **diabetics**, immunocompromised and with obstructive uropathy.
The most common organism is **Proteus mirabilis.**
The definitive treatment is **nephrectomy**.

## Von Hippel-Lindau (VHL) syndrome

It is an autosomal dominant condition resulting from a mutation in the VHL gene, a tumour suppression gene on chromosome 3 leading to (**intracranial**, **eye** and **renal** manifestations):

- **Retinal haemangiomata,**
- **CNS haemangioblastomas (ataxia**, dizziness, unsteadiness),
- **Phaeochromocytoma (↑BP),**
- **Renal cell carcinoma (polycythaemia)**
- Rena cysts (urine blood +, protein +) and
- Pancreatic cysts.

### Diagnosis:

- **MRI brain**
- VHL gene analysis.
- 24 hour VMA (for possibility of Phaeochromocytoma).
- Ophthalmology review.

**EX:** Female Pt 36 years old, with frank haematuria, dizziness, unsteadiness, ataxia, visual problems, F/H of death of her mother at age 40 years, ↑BP, ↑ HB%, abnormal accumulation of vessels in fundus examination, normal creatinine, urine blood + protein + >>> ? **VHL** syndrome >>> for **MRI brain** (the next most important step in her investigations).

## Wilms' tumour (Nephroblastoma)

Wilms' nephroblastoma is one of the most common childhood malignancies. It typically presents in children **< 5 years of age**, with a median age of 3 yrs. old.

### Features:

- **Abdominal mass** (most common presenting feature)
- Painless haematuria
- Flank pain
- Other features: anorexia, fever
- **Unilateral** in 95% of cases
- **Metastases** are found in **20%** of patients (most commonly **lung**)

### Associations:

- **Beckwith-Wiedemann syndrome**
- As part of **WAGR syndrome**: **W**ilms', **A**niridia, **G**enitourinary malformations, mental **R**etardation.
- Hemihypertrophy

- Around one-third of cases are associated with a mutation in the WT1 gene on chromosome 11

**Management:**

- Nephrectomy
- Chemotherapy
- Radiotherapy if advanced disease
- Prognosis: good, 80% cure rate

**NB: Beckwith-Wiedemann syndrome** is an inherited condition associated with organomegaly, macroglossia, abdominal wall defects, Wilm's tumour and neonatal hypoglycaemia.

**NB:** The most common metastatic/**secondary** tumour that produce a **solitary round shadow** in chest cavity is **renal** in origin.

## Phenylketonuria (PKU)

- It is an **autosomal recessive** condition caused by a disorder of phenylalanine metabolism.
- This is due to a **defect** in **phenylalanine hydroxylase**, an enzyme which converts phenylalanine to tyrosine.
- **High levels of phenylalanine** lead to problems such as learning difficulties and seizures.
- The gene for phenylalanine hydroxylase is located on chromosome **12.**
- Phenylketonuria is a quarter as common as congenital hypothyroidism
- The incidence of PKU is 1 in 10,000 live births.

**Features:**

- Usually presents **by 6-12 months** e.g. **with developmental delay.**
- Child classically has **fair hair** and **blue eyes**
- Microcephaly, prominent maxilla, growth retardation and wide-spaced teeth
- **Learning difficulties**
- **Seizures** in 25%, typically **infantile spasms**, over 50% have abnormal EEG.
- **Eczema.**
- **"Musty" odour to urine and sweat**: secondary to phenyl acetate and phenyl ketone.

**Diagnosis:**

- **Guthrie test**: the "heel-prick test" done at 5-9 days of life (Also look for other biochemical disorders such as hypothyroidism).
- **Hyper-phenylalaninemia, increased urinary Phe metabolites.**
- Phenyl pyruvic acid in urine.

## Management:

- **Restriction of dietary phenylalanine**
- Poor evidence base to suggest strict diet prevents learning disabilities.
- Dietary restrictions are however important during pregnancy as genetically normal foetuses may be affected by high maternal phenylalanine levels.

# Alkaptonuria (Black urine disease)

- Rare inherited genetic disorder of phenylalanine and tyrosine metabolism.
- Autosomal recessive.
- Common in Slovakia and Dominican Republic than in other countries.
- Due to a defect in the enzyme homogentisate 1, 2-dioxygenase, which participates in the degradation of tyrosine.
- There is **deficiency of the enzyme homogentisic oxidase** which is responsible of degradation of homogentisic acid produced from phenylalanine and tyrosine.
- As a result, a toxic tyrosine by-product called **homogentisic acid** (or **Alkapton**) accumulates in the blood and is excreted in urine in large amounts.
- Accumulation of homogentisic acid causes pigmentation of the **urine**, **sclera** and **connective tissues**.
- Excessive homogentisic acid causes damage to **cartilage** (ochronosis, leading to osteoarthritis) and **heart valves** as well as precipitating as **kidney stones**.
- Kidney stones and stone formation in the prostate (in men) are common and may occur in more than 25% of cases.
- Alkaptonuria is often asymptomatic, but the **sclera may be pigmented** (often only at a later age), and the **skin may be darkened in sun exposed areas** and around sweat glands; **sweat may be colored brown or black**.
- The main symptoms of Alkaptonuria are due to the accumulation of homogentisic acid in tissues. In the joints this leads to **cartilage damage**, especially in the **spine**, leading to **low back at a young age in most cases**. Cartilage damage may also occur in the **hip and shoulder**. **Joint replacement surgery (hip and shoulder)** is often necessary at a relatively young age.
- **Valvular heart disease**, mainly calcification and regurgitation of the aortic and mitral valves, and in severe and progressive cases **valve**

**replacement** may be necessary. Coronary artery disease may be accelerated in Alkaptonuria.

- Homogentisic acid is a **reducing** agent, therefore it gives a **false positive** Glucostix test (**urine glucose +++**) but normal Clinitest.
- A distinctive characteristics of Alkaptonuria is that **ear wax exposed to air turned red or black** (depending on diet) after several hours because of the accumulation of homogentisic acids.

**Managment:** **Nitisinone** which suppresses homogentisic acid production, is being studied.

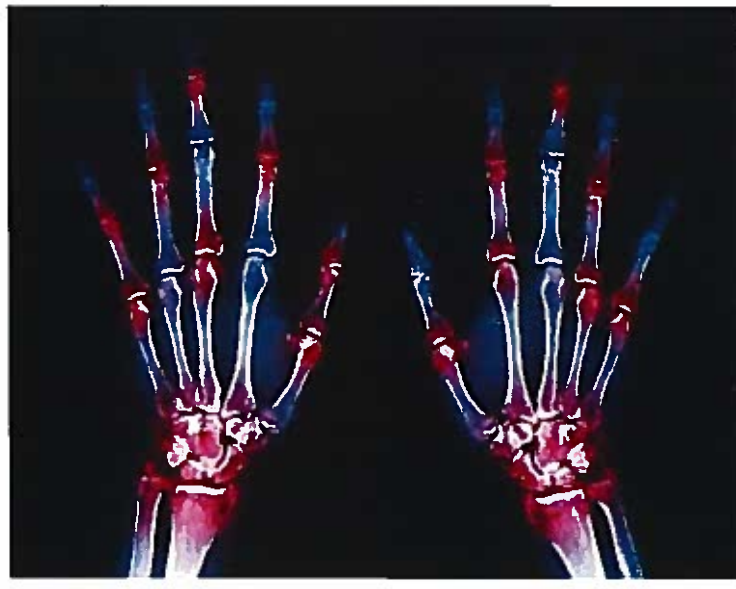
## Retroperitoneal fibrosis

**Lower back pain** is the most common presenting feature.

**Associations:**

- **Riedel's thyroiditis**
- Previous **radiotherapy**
- Sarcoidosis
- **Inflammatory abdominal aortic aneurysm**
- Drugs: methysergide

# Rheumatology



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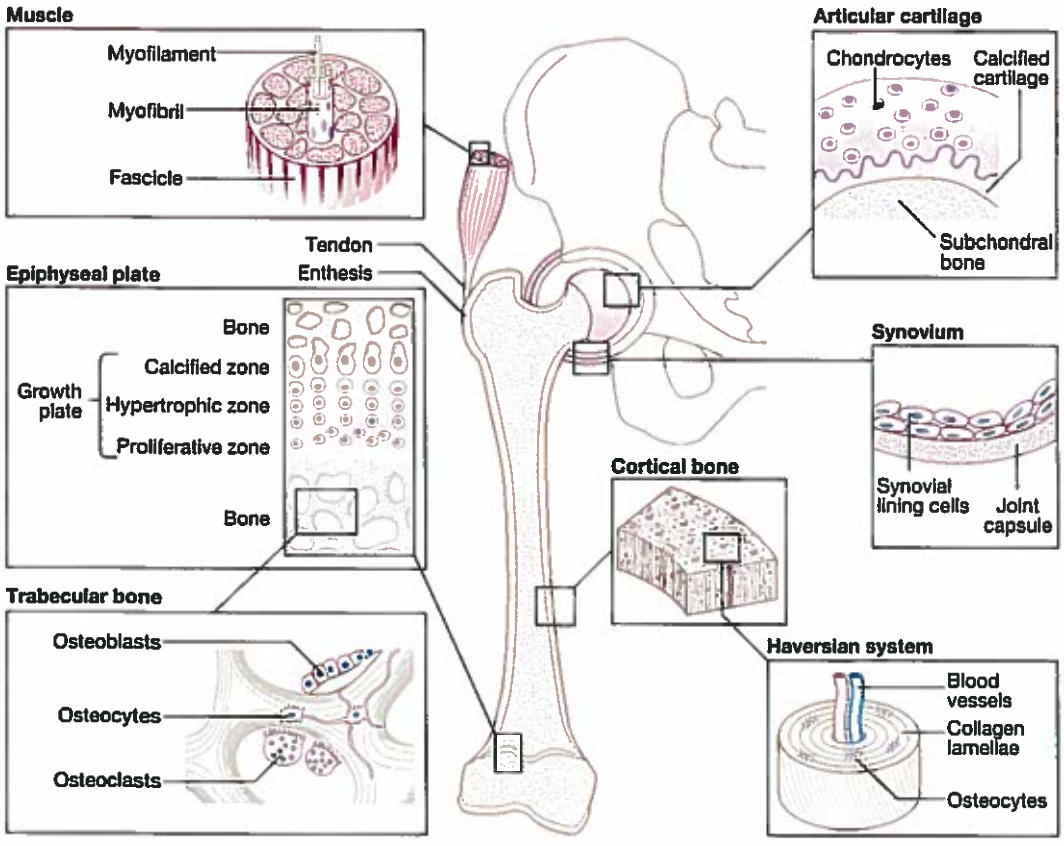
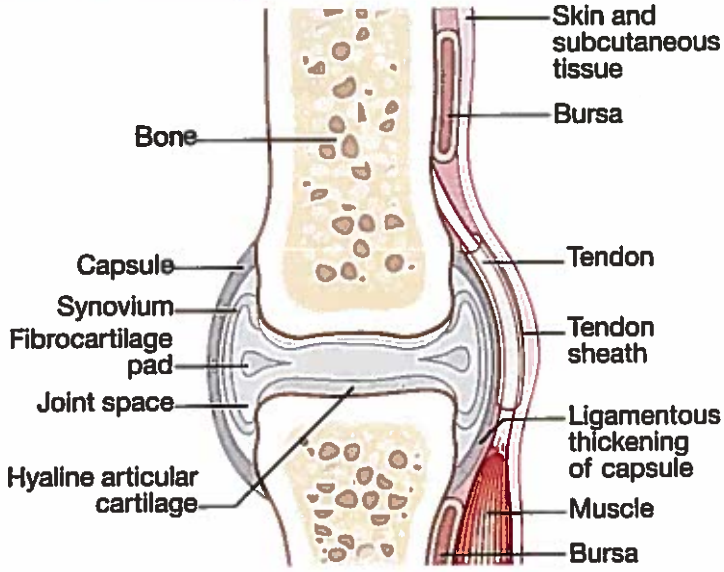
# Basic Anatomy and Physiology



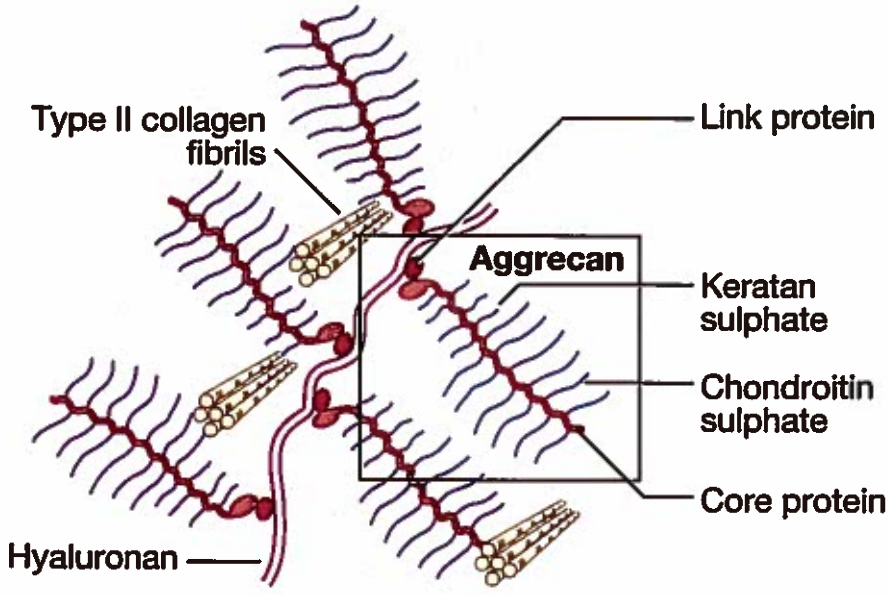

Structure of the major musculoskeletal tissues.




Structure of a synovial joint

## Components of Joint Spaces

| Key regulators of bone remodelling | | | |
|---|---|---|---|
| **Mediator** | **Source** | **Effects** | **Comment** |
| RANKL | Osteocytes<br>Stromal cells<br>Activated T cells | Stimulates bone resorption | Activates RANK |
| Osteoprotegerin | Stromal cells<br>Lymphocytes | Inhibits bone resorption | Acts as decoy receptor for RANKL |
| Wnt | Stromal cells | Stimulates bone formation | Activates LRP receptors |
| Sclerostin | Osteocytes | Inhibits bone formation | Blocks effect of Wnt on LRP receptors |
| Parathyroid hormone | Parathyroid glands | Increases bone resorption and formation | |
| Thyroid hormone | Thyroid gland | Increases bone resorption and formation | |
| Oestrogen | Ovary | Inhibits bone resorption | |
| Glucocorticoid | Adrenal gland<br>Exogenous | Inhibits bone formation | |
| (LRP = lipoprotein receptor-related protein; RANKL = receptor activator of nuclear factor kappa B ligand) | | | |




Ultrastructure of articular cartilage

## Cartilage Ingradients

| Radiographic abnormalities in selected rheumatic diseases | |
|---|---|
| **Rheumatoid arthritis** | |
| • Periarticular osteoporosis<br>• Marginal joint erosions | • Joint subluxation<br>• Joint space narrowing |
| **Osteoporosis** | |
| • Osteopenia<br>• Vertebral fractures | • Non-vertebral fractures<br>• Cortical thinning |
| **Paget's disease** | |
| • Bone expansion<br>• Abnormal trabecular pattern | • Osteosclerosis and lysis<br>• Pseudofractures |
| **Psoriatic arthritis** | |
| • Sacroiliitis<br>• Syndesmophytes<br>• Bone sclerosis | • Proliferative enthesis erosions<br>• Enthesophytes<br>• Juxta-articular new bone |
| **Osteoarthritis** | |
| • Joint space narrowing<br>• Osteophytes<br>• Subchondral sclerosis | • Joint deformity<br>• Subchondral cysts |

# Lab evaluation

## Rheumatoid factor (RF)

Rheumatoid factor (RF) is a circulating antibody (usually IgM) which reacts with the **Fc** portion of the patients own **IgG**.

Rheumatoid factor is an **IgM** antibody with reactivity **against Fc portion of IgG**

**RF can be detected by either:**

- Rose-Waaler test: sheep red cell agglutination
- Latex agglutination test (less specific)

RF is positive in **70-80% of patients with rheumatoid arthritis**; high titre levels are associated with severe progressive disease (but **NOT** a marker of disease **activity**).

### A positive rheumatoid factor is associated with:

- More severe erosive disease
- Extra-articular manifestations including subcutaneous nodules and
- Increased mortality.

### Other conditions associated with a positive RF include:

- Sjogren's syndrome (around **100%**)
- Felty's syndrome (around **100%**)
- Infective endocarditis (= **50%**)
- Mixed cryoglobulinaemia (types II and III) (**40 to 100%**)
- SLE (= **20-30%**)
- Systemic sclerosis (= 30%)
- Polymyositis/dermatomyositis - 5 to 10%
- General population (= 5%)
- Rarely: TB, HBV, HIV, EBV, leprosy, syphilis, brucellosis.

In RA, RF is positive in 80% of patients, whereas in Sjogren's syndrome and cryoglobulinaemia, it is prevalent in up to 90% of cases.

## Anti-CCP Ab (Anti-cyclic citrullinated peptide antibodies)

**Anti-CCP antibodies** are associated with rheumatoid arthritis (**highly specific**)

- Anti-cyclic citrullinated peptide antibody may be detectable **up to 10 years before** the development of rheumatoid arthritis.
- It may therefore play a key role in the future of rheumatoid arthritis, allowing **early detection** of patients suitable for aggressive anti-TNF therapy.
- It has sensitivity similar to rheumatoid factor (70-80%, see below) with **a much higher specificity** of 90-95%.
- NICE recommends that patients with suspected RA with RF negative
- should be tested for Anti-CCP Abs.

## Extractable nuclear antigens

### Overview:

- specific nuclear antigens
- usually associated **with being ANA positive**

### Examples:

- **Anti-Ro:** Sjogren's syndrome, SLE, congenital heart block
- **Anti-La:** Sjogren's syndrome
- **Anti-Jo 1: polymyositis** (more than Dermatomyositis)
- **Anti-centromere**: limited cutaneous systemic sclerosis
- **Anti-scl-70 (Anti-topoisomerase I):** diffuse cutaneous systemic sclerosis

# Tumour necrosis factor (TNF)

Rheumatoid arthritis - TNF is key in pathophysiology

TNF is important in the pathogenesis of rheumatoid arthritis.
**TNF blockers (e.g., infliximab, etanercept)** are now licensed for treatment of severe RA.

**TNF** is a **pro-inflammatory cytokine** with multiple roles in the immune system.

**TNF** is secreted mainly by **macrophages** and has a number of effects on the immune system, acting mainly in a paracrine fashion:

- Activates macrophages and neutrophils
- Acts as co-stimulator for T cell activation
- Key mediator of bodies response to Gram negative septicaemia
- Similar properties to IL-1
- Anti-tumour effect (e.g. phospholipase activation)

TNF-alpha binds to both the p55 and p75 receptor. These receptors can induce apoptosis. It also causes activation of NFkB.

Endothelial effects include increase expression of selectins and increased production of platelet activating factor, IL-1 and prostaglandins.

TNF promotes the proliferation of fibroblasts and their production of protease and collagenase. It is thought fragments of receptors act as binding points in serum.

Systemic effects include pyrexia, increased acute phase proteins and disordered metabolism leading to cachexia.

**Contraindications of usage of TNF- alpha antagonist:**

- Active infection
- **Active TB**
- **MS** (Multiple sclerosis)
- Heart failure (NYHA grade 3-4).
- Pregnancy
- Breast feeding

## TNF inhibitors

TNF is important in the pathogenesis of a number of inflammatory conditions such as **rheumatoid arthritis** and Crohn's disease.
TNF inhibitors are therefore now used for a variety of conditions.

### Examples of TNF inhibitors

- infliximab: monoclonal antibody, IV administration
- etanercept: fusion protein that mimics the inhibitory effects of naturally occurring soluble TNF receptors, subcutaneous administration
- adalimumab: monoclonal antibody, subcutaneous administration
- golimumab: subcutaneous administration
- adverse effects of TNF blockers include reactivation of latent tuberculosis and demyelination

Infliximab is also used in active Crohn's disease unresponsive to steroids

## Bone markers

Bones are now recognised to be metabolically active, dynamic tissues, rather than merely acting as a skeletal structure and reservoir for mineral ions.

Interest in diseases such as osteoporosis has stimulated the search for markers of bone turnover.

Markers are useful for prediction of prognosis, prediction of fracture risk, assessing suitability for therapy and monitoring the success of therapy.

| Markers of **bone formation** (are measured in serum) | Markers of **bone resorption** (are measurable in serum or urine) |
|---|---|
| ➢ **Bone-derived alkaline phosphatase (ALP).**<br>➢ Osteocalcin and<br>➢ Procollagen type 1 propeptides. | ➢ Telopeptides (NTx and CTx)<br>➢ Pyridinium cross-linking molecules<br>➢ Tartrate-resistant acid phosphatase (TRAP) and<br>➢ Hydroxyproline. |

Alkaline phosphatase is useful but not specific to bone.

Osteocalcin is the main non-collagenous protein in bone. During bone formation, osteoblasts make osteocalcin and release some of it into the circulation. Resorption may cause a smaller increase in serum osteocalcin.

Collagen is made from procollagen, with cleavage of N- and C-terminal peptides. These peptides can be measured but are not as sensitive or specific as bone alkaline phosphatase.

## Bone disorders: lab values

| Disorder | Calcium | Phosphate | ALP | PTH |
|---|---|---|---|---|
| **Osteoporosis** | Normal | Normal | Normal | Normal |
| **Osteomalacia** | Decreased | Decreased | Increased | Increased |
| **Primary hyperparathyroidism** (→ osteitis fibrosa cystica) | Increased | Decreased | Increased | Increased |
| **Chronic kidney disease** (→ secondary hyperparathyroidism) | Decreased | Increased | Increased | Increased |
| **Paget's disease** | Normal | Normal | Increased | Normal |
| **Osteopetrosis** | Normal | Normal | Normal | Normal |

### Causes of recurrent arthritis:

- **Crystal arthritis** (gout or Pseudogout): the most common cause of recurrent arthritis.
- Systemic auto inflammatory disorders (periodic fever syndromes).
- Whipple's disease.
- Arthritis associated with hyperlipidaemia.
- Intermittent hydrarthrosis.

**EX**: Pt with recurrent arthritis but now is free >>> **ask the patient to report to the clinic during the next attack** >>? **Crystal** arthritis for **aspiration** during the attack

# Drug therapy

## Methotrexate

Methotrexate is an antimetabolite which **inhibits dihydrofolate reductase (DHFR enz)**, an enzyme essential for the synthesis of purines and pyrimidines.

### Indications:

- **Rheumatoid arthritis**
- **Psoriasis**
- Acute lymphoblastic leukaemia

### Adverse effects:

- **Hepatitis** and Liver cirrhosis
- **Myelosuppression**
- **Pneumonitis**
- **Pulmonary fibrosis**
- Mucositis

### Pregnancy:

- Women should **avoid pregnancy for at least 3 months after** treatment has stopped.
- The BNF also advises that **men using methotrexate** need to use **effective contraception** for at **least 3 months after** treatment.

Men and women should avoid pregnancy for at least **3 months after** MTX has stopped.

### Prescribing methotrexate:

- Methotrexate is a drug with a high potential for patient harm. It is therefore important that you are familiar with guidelines relating to its use.
- Methotrexate is taken **weekly,** rather than daily.
- **Dose starting from 7.5 mg up to 20 mg per week.**
- **FBC, U&E** and **LFTs** need to be regularly monitored.
- The Committee on Safety of Medicines recommend 'FBC and renal and LFTs **before starting** treatment and repeated **weekly** until therapy stabilised, thereafter patients should be **monitored every 2-3 months'.**

- **Folic acid 5mg once daily** should be co-prescribed, taken **more than 24 hours after** methotrexate dose.
- Only one strength of methotrexate tablet should be prescribed (usually 2.5 mg).
- Methotrexate is recognised to be associated with pulmonary fibrosis. **Baseline pulmonary function tests (PFTs)** are recommended prior to starting therapy, and physicians are warned to be alert to increased shortness of breath.

## Interactions

- avoid prescribing **trimethoprim** or co-trimoxazole concurrently - increases risk of marrow aplasia
- high-dose **aspirin** increases the risk of methotrexate toxicity secondary to reduced excretion

## Methotrexate toxicity

- the treatment of choice is folinic acid

**NB**: Methotrexate is a folic acid antagonist which can result in **multi-organ failure** in **overdose**.

## More details about toxicity and its treatment

**Folinic acid** (**Calcium folinate**) (**Leucovorin**) **IVI** is the **antidote** for the effect of methotrexate on the **haematopeic system** and should be given **IV infusion as soon as possible**, **regardless** of the liver function tests, Dose: 75 mg in the first 12 hrs, and can then be followed by 6-12 mg every 4 hrs.

**Blood transfusion** may be required in exceptional circumstances.

Supportive measures by **good hydration** and **urinary alkalinization** may be used.

Standard dialysis is ineffective in removing methotrexate, although **intermittent high flux dialysis** may be of value.

**If white cell count is less than 3.5, neutrophils less than 2** or **platelets less than 150**, methotrexate should be **withheld** pending discussion with the specialist team.

An **MCV greater than 105 fL** warrants checking B12, folate and TSH and treating any abnormality. If these are normal, discuss with the specialist team.

**Liver function tests** should be **checked.** If there is an unexplained decrease in albumin, or AST/ALT twice the upper limit of normal, the specialist team should be informed.

**Urea, creatinine and electrolytes** should be **checked**. If the eGFR falls below 50 mL/minute, methotrexate should be withheld until the result be discussed with the specialist team.

**In addition to this monitoring, any clinical signs of toxicity should be monitored** for. If the patient develops rash, oral ulceration, sore throat, easy bruising or bleeding, shortness of breath, abdominal pain, nausea, vomiting, diarrhoea or jaundice, methotrexate should be withheld until discussed with the specialist team. **It should be documented in patient notes that this advice has been given.**

A sore throat or abnormal bruising should be investigated with an FBC, and methotrexate withheld until the results available.

In the setting of **acute infection, most DMARDs (except hydroxychloroquine)** should be **discontinued until** the infectious process has resolved.

So patient on **methotrexate** and develop **lower respiratory tract infection** with **normal** CXR, CBC, LFTs, U&E.

The most appropriate action is > **Stop methotrexate temporarily + Antibiotics (oral/IV).**

**Methotrexate-related lung toxicity**: a large spectrum of diseases ranging from **interstitial pneumonitis** to cough, pleuritic chest pain and SOB related to lung infiltration, associated with bilateral pleural effusions.

**Treatment: Methotrexate withdrawal** and **replace** with anti-TNF or anti-CD20 antibody.

# Sulfasalazine

Sulfasalazine is a disease modifying anti-rheumatic drug (DMARDs) used in the management of inflammatory arthritis, especially rheumatoid arthritis.
It is also used in the management of inflammatory bowel disease.

Sulfasalazine is a prodrug for 5-ASA which works through decreasing neutrophil chemotaxis alongside suppressing proliferation of lymphocytes and pro-inflammatory cytokines.

Current UK guidance suggests that during the first 3 months of treatment with sulfasalazine, **CBC** should be monitored **monthly** for **the first 3 months**.

**Sulphasalazine** should be withheld until discussion with the specialist team if:

- The white cell count is less than 3.5
- Neutrophils is less than 2, or
- Platelets are less than 150.

If mean corpuscular **volume (MCV) is more than 105 fl**, vitamin **B12**, **folate** and **TSH** should be checked and treated if found to be abnormal. If these are all normal it should be discussed with the specialist team.

If counts remain normal within the first 3 months, **CBC can be checked 3 monthly.**

Liver function tests (**LFTs**) should also be checked **monthly** for the first 3 months. If either AST or ALT are **more than twice the upper limit** of normal, sulfasalazine should be **withheld** until discussion with the specialist team.

If the LFTs remain normal for the first 3 months, monitoring can be decreased **to 3 monthly**.

If, following the first year, the dose has not been increased and blood results have been stable, the frequency of monitoring can be reduced to **every six months** for the second year of treatment. Thereafter monitoring is not required, although CBC and LFTs should be checked one month after any dose increase.

**Side effects of sulfasalazine** include **hypersensitivity, myelosuppression, macrocytosis**, and **azoospermia in males.**

**There are numerous signs of sulfasalazine toxicity.**
Rash and oral ulceration should be asked about and, if severe, the drug should be withheld until specialist advice has been sought.
Nausea, dizziness and headache can be common and sometimes necessitate dose reduction.
If patients present with abnormal bruising or sore throat an urgent CBC should be done, and sulfasalazine withheld until results are available.

In contrast to other DMARDs, sulfasalazine is considered **safe to use in both pregnancy and breastfeeding.**

## Leflunomide (Arava® 20 mg tab)

Leflunomide is a disease modifying anti-rheumatic drug (DMARD) mainly used in the management of rheumatoid arthritis. It has a very long half-life which should be remembered considering it's teratogenic potential.

- Leflunomide is associated with serious **hepatotoxicity**.
- Increased aminotransferases are commonly seen in association with therapy occurring in 15-20% of cases (**less than a twofold rise**).
- However, **more serious elevation (greater than threefold)** is seen in less than 5%.
- Generally, most hepatic events occur within the first 6 months of use. It is recommended liver function tests (**LFTs**) be checked **monthly** for 6 months and, if stable, **2 monthly thereafter**.
- **If** AST or ALT is **between 2 and 3 times the upper limit** of normal, and the leflunomide dose is more than 10 mg daily, the dose should be **reduced to 10 mg** and **LFTs rechecked weekly** until normalised. If the ALT and AST are returning to normal, the patient should be left on 10 mg per day. It the LFTs remain elevated, leflunomide should be stopped and discussed with the specialist team.
- **If** the AST or ALT is **more than 3 times the upper limit** of normal, the **LFTs should be rechecked within 72 hours.** If they **remain** more than 3 times the reference range, leflunomide should be **stopped** and **washout** considered (cholestyramine and activated charcoal).
- It is important to note that the **half-life of leflunomide is usually 2 weeks** (mean 1-4) therefore if a rapid response is required, washout should be considered.
- Current UK guidance also recommends frequent monitoring for patients on leflunomide. Full blood count (**CBC**) should be checked **monthly** for six months and, if stable, two monthly thereafter.
- White cell count less than 3.5, neutrophils less than 2 or platelets less than 150 should be discussed with the specialist team, and leflunomide withheld until this has taken place.
- Monitoring should be continued at least monthly in the long term if leflunomide is co-prescribed with any other immunosuppressant or potentially hepatotoxic agent.

- In addition, **signs of leflunomide toxicity** should be monitored. If the patient develops a rash or itch dose reduction should be considered, with or without the addition of antihistamines. If severe, leflunomide should be stopped and washout considered.
- Hair loss, headaches and gastrointestinal upset may also warrant dose reduction or washout.
- A blood pressure of greater than 140/90 mmHg should be treated as per NICE guidelines. If it remains elevated, stop leflunomide and consider washout.
- Weight should be monitored, and a weight loss of greater than 10% should be identified. If no other cause can be found, consider dose reduction or washout.
- If there is increasing shortness of breath, pneumonitis should be considered and leflunomide should be stopped.

**Leflunomide reduces sperm count.**

## Azathioprine (Imuran)

Azathioprine is metabolized to the active compound mercaptopurine, a purine analogue that **inhibits purine synthesis** (inhibits DNA synthesis).
A **thiopurine methyltransferase (TPMT) test** may be needed to look for individuals prone to azathioprine toxicity.

**Azathioprine** - check **thiopurine methyltransferase deficiency (TPMT)** before treatment

Thiopurine methyltransferase (TPMT) deficiency is present in about **1 in 300** people and predisposes to azathioprine related pancytopenia.

The enzyme activity of TPMT is under the control of a genetic polymorphism.
**90%** of the population have **normal or high enzyme activity**, that is, are homozygous for the wild-type allele.
**10%** of the population have **intermediate** levels of TPMT activity, that is, one wild-type and one variant allele.
**One** in **300** people have **no** functional enzyme activity.

### Adverse effects include:

- **Bone marrow depression >>> Pancytopenia**
  - **consider a full blood count if infection/bleeding occurs**
- **Hepatotoxicity**

- **Pancreatitis**
- Nausea/vomiting
- increased risk of non-melanoma skin cancer

A significant interaction may occur with **allopurinol** and hence **lower doses of azathioprine should be used** (so you may give only 25% of the usual dose of azathioprine).

The prodrug azathioprine is metabolised to its active compound 6-mercaptopurine (6-MP). 6-MP undergoes catabolic oxidation to 6-thiouric acid by xanthine oxidase.

Allopurinol has a peak onset of action of one to two weeks and works by inhibiting xanthine oxidase.

Co-administration of these drugs **(Imuran + Allopurinol)** may lead to **accumulation of 6-MP (6-MP toxicity)** and increases the **risk of myelosuppression (aplastic anaemia)**. ☹

The newer xanthine oxidase inhibitor, **Febuxostat**, can also result in the same problem and is also contraindicated.

Febuxostat is a **non-purine, selective xanthine oxidase inhibitor** unlike allopurinol, which is a purine analogue inhibitor of xanthine oxidase.

Current guidelines from the British Association of Dermatologists and the British National Formulary (BNF) suggest **monitoring CBC, LFTs and U&E every 3 months** once patients are established and stable on azathioprine treatment.

## Hydroxychloroquine

Hydroxychloroquine is used in the management of rheumatoid arthritis and systemic/discoid lupus erythematosus.
It is pharmacologically very similar to chloroquine which is used to treat certain types of malaria.

**Hydroxychloroquine ocular toxicity includes:**

- Keratopathy
- Ciliary body involvement
- Lens opacities (**Lenticular deposits**)
- **Retinopathy**.

Retinopathy is the major concern; the others are more common but benign.

**The incidence of true hydroxychloroquine retinopathy is exceedingly low.**
**Risk factors include:**

- Daily dosage of hydroxychloroquine
- Cumulative dosage
- Duration of treatment
- Coexisting renal or liver disease
- Patient age, and
- Concomitant retinal disease.

Patients usually complain of difficulty in reading, decreased vision, missing central vision, glare, blurred vision, light flashes, and metamorphopsia. They can also be asymptomatic.

Most patients with advanced retinopathy have a **bull's eye** (also known as target, as in darts) fundoscopic appearance.
All patients have field defects including **para-central, peri-central, and central and peripheral field loss.**

Regular screening may be necessary to detect reversible premaculopathy.

A contrast to many drugs used in rheumatology, hydroxychloroquine may be used if needed in pregnant women.

## Vitamin D supplementation

Vitamin D supplementation has been a hot topic for a number of years now. The muddied waters are now slightly clearer following the release of the

**following:**

- 2012: letter by the Chief Medical Officer regarding vitamin D supplementation
- 2013: National Osteoporosis Society (NOS) release UK Vitamin D guideline

**The following groups should be advised to take vitamin D supplementation:**

- all pregnant and breastfeeding women should take a daily supplement containing 10µg of vitamin D
- all children aged 6 months - 5 years. Babies fed with formula milk do not need to take a supplement if they are taking more than 500ml of milk a day, as formula milk is fortified with vitamin D
- adults > 65 years
- 'people who are not exposed to much sun should also take a daily supplement' e.g. housebound patients

## Testing for vitamin D deficiency

The key message is that not many people warrant a vitamin D test. The NOS guidelines specify that testing may be appropriate in the following situtations:

- patients with bone diseases that may be improved with vitamin D treatment e.g., known osteomalacia or Paget's disease
- patients with bone diseases, prior to specific treatment where correcting vitamin deficiency is appropriate e,g, prior to intravenous zolendronate or denosumab
- patients with musculoskeletal symptoms that could be attributed to vitamin D deficiency e.g., bone pain? osteomalacia

Patients with osteoporosis should always be given calcium/vitamin D supplements so testing is not considered necessary.
People who are at higher risk of vitamin D deficiency (see above) should be treated anyway so again testing is not necessary.

### Treatment criteria for patients not taking alendronate:

Unfortunately, a number of complicated treatment cut-off tables have been produced in the latest guidelines for patients who do not tolerate alendronate.

These take into account a patients age, their T-score and the number of risk factors they have from the following list:

- Parental history of hip fracture
- Alcohol intake of 4 or more units per day
- Rheumatoid arthritis

It is very unlikely that examiners would expect you to have memorised these risk tables so we've not included them in the revision notes but they may be found by following the NICE link. The most important thing to remember is:

- The T-score criteria for risedronate or etidronate are less than the others implying that these are the second line drugs
- If alendronate, risedronate or etidronate cannot be taken then strontium ranelate or raloxifene may be given based on quite strict T-scores (e.g. a 60-year-old woman would need a T-score < -3.5)
- The strictest criteria are for denosumab

## Supplementary notes on treatment:

### Bisphosphonates:

- Alendronate, risedronate and etidronate are all licensed for the prevention and treatment of post-menopausal and glucocorticoid-induced osteoporosis.
- All three have been shown to reduce the risk of both vertebral and non-vertebral fractures although **Alendronate (Fosamax® 70 mg tab**

once weekly), Risedronate (Actonel ® 35 mg tab once weekly) may be superior to etidronate in preventing hip fractures.
- Ibandronate Na (Boniva® 150 mg tab) is a once-monthly oral bisphosphonate.
- Despite daily, weekly, or monthly dosing, patients still suffer significant symptoms of indigestion (oesophagitis).

## Tamoxifen

Tamoxifen is a Selective Oestrogen Receptor Modulator (**SERM**) which acts as an oestrogen receptor **antagonist** and partial **agonist**.

It has both **oestrogen-like activity** at sites like **bone** (to increase mineralisation), but **anti-oestrogen-like effects** on **breast/endometrium** (preventing breast/endometrial hyperplasia).

It is used in the management of **oestrogen receptor positive breast cancer**.

It is usually taken **orally once a day** for **up to 5 years following removal of the tumour**, but for patients with metastatic disease it can be continued longer.

After surgical intervention, tamoxifen **reduces the risk of recurrence** of ductal carcinoma in situ and early stage invasive disease.

It confers a survival advantage of up to 4 years in postmenopausal women, and so it is given usually for 5 years after diagnosis.

It is even effective in women who **do not have a personal history** of breast cancer but who are **at increased risk** of the disease.

Due to its weak Oestrogen like properties: **slight decrease in total cholesterol** in postmenopausal women ☺ and **increase bone density** ☺

**Adverse effects (due to the weak Oestrogen like properties)** ☹
- ↑ **Risk of Venous thromboembolism.**
- ↑ **Risk of Endometrial cancer.**
- **Medical menopause:** in the form of **menstrual disturbance**: vaginal bleeding, amenorrhoea and **hot flushes.**
- **Indigestion and feeling sick**
- **Weight gain**
- **Vaginal dryness**
- **Vaginal discharge**
- **Alopecia**
- **Cataract**

**Tamoxifen-induce medical menopause** with symptoms mimic to postmenopausal women like **amenorrhoea** and **hot flushes** which can be managed by adding **Megestrol** (Megace ®) , Medroxyprogesterone (Provera ®) and Norethisterone (Primolut N, Utovlan ®) ± antidepressants in low doses (SSRIs).
Hormone replacement therapy is not usually offered to women who have had breast cancer as it may increase the risk of breast cancer returning.

**Raloxifene** is a pure oestrogen receptor antagonist, and carries a lower risk of endometrial cancer.

## Bisphosphonates

Bisphosphonates are analogues of pyrophosphate, a molecule which decreases demineralisation in bone.
They **inhibit osteoclasts** by reducing recruitment and promoting apoptosis.
It is the **first** choice therapy for osteoporosis.

Bisphosphonates >>> **Inhibit osteoclasts**

### Clinical uses:

- Prevention and treatment of osteoporosis
- Hypercalcaemia
- Paget's disease
- Pain from bone metastases

### Adverse effects

- **oesophageal reactions:** oesophagitis, oesophageal ulcers (especially alendronate)
- **osteonecrosis of the jaw**
- increased risk of **atypical stress fractures** of the proximal femoral shaft in patients taking alendronate
- acute phase response: fever, myalgia and arthralgia may occur following administration
- hypocalcaemia: due to reduced calcium efflux from bone. Usually clinically unimportant

**The BNF suggests the following counselling for patients taking oral bisphosphonates**

'Tablets should be swallowed whole with **plenty of water** while **sitting or standing**; to be given on an **empty stomach** at least **30 minutes before breakfast** (or another oral medication); patient should **stand or sit upright for at least 30 minutes after** taking tablet'

Guidelines for osteoporosis recommend prescription of a **weekly generic bisphosphonates firstly**. For patients who fail to tolerate a weekly preparation, monthly oral or more intermittent IV preparations may be appropriate.

### Calcitonin:

- Exogenous calcitonin **inhibits osteoclast activity**, and is associated with a 1-2% increase in BMD which is sustained for up to five years.
- Calcitonin is associated with a marked decrease in bone turnover, and consequently a decrease in urinary hydroxyproline excretion.
- In the absence of ADH, calcitonin increases sodium, potassium, calcium, and magnesium and chloride tubular resorption, thereby reducing their urinary excretion. It also decreases urinary hydroxyproline excretion.
- Rarely used due to **anaphylaxis**

### Vitamin D and calcium:

- Poor evidence base to suggest reduced fracture rates in the general population at risk of osteoporotic fractures - may reduce rates in frail, housebound patients.

### Raloxifene - Selective Estrogen Receptor Modulator (SERM): ☺

- Like tamoxifen is a SERM, with **oestrogen-like activity** at sites like **bone** (to increase mineralisation), but **anti-oestrogen-like effects** on **breast/endometrium** (preventing breast/endometrial hyperplasia).
- Has been shown to **prevent bone loss** and to **reduce the risk of vertebral fractures**, but has not yet been shown to reduce the risk of non-vertebral fractures.
- It increase bone density in the spine and proximal femur.
- May **worsen menopausal symptoms**
- **Increased risk of thromboembolic events**
- May **decrease** **risk of breast /endometrium cancer** ☺

### Strontium ranelate:

- **'Dual action bone agent'** - increases deposition of new bone by osteoblasts (promotes differentiation of pre-osteoblast to osteoblast) and reduces the resorption of bone by inhibiting osteoclasts.
- Strong evidence base, may be second-line treatment in near future
- Increased risk of **thromboembolic** events

### Denosumab (XGEVA 120 mg vial,PROLIA 60 MG ®AMGEN CO):

- Human **monoclonal antibody** that inhibits the nuclear factor-kappa ligand (**RANK ligand inhibitor**) involved in osteoclast activation, which in turn **inhibits the maturation of osteoclasts**.

- RANK occurs on the surface of osteoclast precursors and osteoclasts. Inhibiting it leads to reduced osteoclast formation, function and survival. This leads to reduced bone reabsorption in both cortical and trabecular bone.
- It is as effective as intermittent bisphosphonate therapy and **inhibits pre-osteoclasts and osteoclasts.**
- Given as a **single SC** injection **every 6 months.**
  A larger dose of denosumab (120mg) may also be given every 4 weeks for the prevention of skeletal-related events (i.e. pathological fractures) in adults with bone metastases from solid tumours. For example, you may have noticed some of your breast cancer patients have been prescribed denosumab.
- It is having a **40% reduction** in the **risk of hip fracture over 3 years.**

## Where does it fit in the management of osteoporosis?

- Oral bisphosphonates are still given first-line, with oral alendronate being the first-line treatment.
- If alendronate is not tolerated then NICE recommend using an alternative bisphosphonate - either risedronate or etidronate.
- Following this the advice becomes more complicated with the next-line medications only being started if certain T score and other risk factor criteria being met.
- Raloxifene and strontium ranelate were recommended as next-line drugs in the NICE criteria but following recent safety concerns regarding strontium ranelate it is likely there will be an increasing role for denosumab.
- NICE published a technology appraisal looking at the role of denosumab in 2010. A link is provided.

## What are the known side-effects of denosumab?

- Denosumab is generally well tolerated.
- Dyspnea and diarrhea are generally considered the two most common side effects, occurring in around 1 in 10 patients.
- Other less common side effects include hypocalcemia and upper respiratory tract infections.

## What does the Drug Safety Update add?

- Cases of atypical femoral fractures have been noted in patients taking denosumab.
- Doctors are advised to look out for patients complaining of unusual thigh, hip or groin pain.

**EX**: Old female 77 years old with **severe osteoporosis**, T score was measured at **-4.2**, she has suffered a previous **Colles' fracture**, and has a history of a **previous left leg DVT**. She was **unable to tolerate weekly alendronate** due to symptoms of **severe reflux esophagitis**.

The most appropriate alternative for her is >>> **Six monthly denosumab SC.**

**Teriparatide SC**:

- Recombinant form of PTH.
- It is synthetic PTH analogue.
- It is given SC injection.
- **Increased osteoblast activity**
- Very effective at increasing bone mineral density but role in the management of osteoporosis yet to be clearly defined.

**Hormone replacement therapy (HRT):**

- Has been shown to reduce the incidence of vertebral fracture and non-vertebral fractures.
- Due to concerns about increased rates of cardiovascular disease and breast cancer it is no longer recommended for primary or secondary prevention of osteoporosis unless the woman is suffering from vasomotor symptoms.
- **Unopposed oestrogen therapy** is most appropriate if patient has had a **hysterectomy and oophorectomy,** and combined hormone replacement therapy (HRT) is unnecessary.
- Tibolone, Raloxifine and bisphosphonates are recommended as second line agents where HRT may be poorly tolerated or contra-indicated.

**Hip protectors:**

- Evidence to suggest significantly reduce hip fractures in nursing home patients
- Compliance is a problem

**Falls risk assessment:**

- No evidence to suggest reduced fracture rates
- However, do reduce rate of falls and should be considered in management of high risk patients

**EX**: A previously fit **47-year-old male** presents with lower back pain from a vertebral collapse due to **osteoporosis**.
Which is the most appropriate investigation for this man? **Testosterone**

**Osteoporosis** in a **young male** would be unusual >> **check testosterone**

## Penicillamine

### Mechanism of action

- largely unknown
- thought to reduce IL-1 synthesis and prevent the maturation of newly synthesized collagen

### Uses

- rheumatoid arthritis

### Adverse effects

- rashes
- disturbance of taste
- proteinuria

## Mycophenolate mofetil

Mycophenolate mofetil is an immunosuppressant commonly used to prevent rejection of organ transplants.

### Mode of action

- inhibits inosine monophosphate dehydrogenase, which is needed for purine synthesis
- as T and B cells are particularly dependent on this pathway it can reduce the proliferation of immune cells.

# Introduction topics

## Polyarthritis

### Differential diagnosis

- rheumatoid arthritis
- SLE
- seronegative spondyloarthropathies
- Henoch-Schonlein purpura
- sarcoidosis
- tuberculosis
- pseudogout
- viral infection: EBV, HIV, hepatitis, mumps, rubella

## Complex regional pain syndrome (CRPS)

CRPS is a **chronic pain** condition that can affect **any area of the body**, but often affects an arm or a leg, and occurs **after an injury** or **rarely after a sudden illness** such as a heart attack or stroke.

It is the modern, umbrella term for a number of conditions such as **reflex sympathetic dystrophy and causalgia.**

It describes a number of neurological and related symptoms which typically occur following surgery or a minor injury.

CRPS is **3 times** more common in **women**.

The condition can sometimes appear without obvious injury to the affected limb.

**CRPS has two forms:**

- **CRPS I** occurs in the absence of a preceding nerve injury (**NO** nerve injury)
- **CRPS II** is caused by an **injury** to the **nerve**.

**The key symptom is pain that:**

- Is intense and burning
- Is disproportionate to the original injury
- Is worse over time
- Spreads beyond the site of injury and
- Is associated with hyperalgesia, hyperpathia or allodynia on examination. These features do not occur in DVT, osteomyelitis, or cellulitis.

## Features:

- **Progressive, disproportionate symptoms** to the **original** injury/surgery.
- Allodynia.
- **Temperature** and **skin** colour changes
- **Oedema** and sweating
- Motor dysfunction
- The Budapest Diagnostic Criteria are commonly used in the UK

**CRPS may have 3 stages** (acute, dystrophic, and atrophic), with variable progression from one stage to another.

**CRPS is a clinical diagnosis**, and various imaging modalities show non-specific changes which support its diagnosis:

- Plain radiographs may show soft tissue swelling, peri-articular osteoporosis, and rarely erosions.
- MRI may also show bone marrow oedema apart from these changes.
- 99mTc bone scan shows hypervascularity in the acute phase, and hypovascularity in the atrophic phase.

In the atrophic phase, imaging may show contractures.

## Management:

- **Early physiotherapy** is important.
- **Neuropathic analgesia** in-line with NICE guidelines.
- Specialist management (e.g. Pain team) is required.

**EX:** A 38-year-old woman comes for review. Six months ago she fractured her left wrist whilst skiing. The fracture was treated using a cast and repeat x-rays showed that the bone had healed well. Unfortunately for the past few weeks she has been plagued with ongoing 'shooting pains' in her left hand associated with swelling. On examination the left hand is extremely tender to even light touch. Her left hand is also slightly swollen compared to the right.

What is the most likely diagnosis? >>>> **CRPS**.

## Shoulder problems

The table below summarizes the key features of common shoulder problems:

| Condition | Notes |
|---|---|
| **Adhesive capsulitis (frozen shoulder)** | Common in middle-age and diabetics<br>Characterized by painful, stiff movement<br>Limited movement in all directions, with loss of external rotation and abduction in about 50% of patients |
| **Supraspinatus tendonitis (Subacromial impingement, painful arc)** | Rotator cuff injury<br>Painful arc of abduction between 60 and 120 degrees<br>Tenderness over anterior acromion |

## Adhesive capsulitis

**Management:**

- no single intervention has been shown to improve outcome in the long-term
- treatment options include NSAIDs, physiotherapy, oral corticosteroids and intra-articular corticosteroids

**NB:** Diabetic amyotrophy affects the lower limbs

# Elbow pain

The table below details some of the characteristic features of conditions causing elbow pain:

| | |
|---|---|
| Lateral epicondylitis (tennis elbow) | **Features**<br>• It is most common in people aged 45-55 years and typically affects the **dominant arm.**<br>• Typically follows unaccustomed activity such as house painting or playing tennis ('tennis elbow').<br>• It is due to overuse/strain of the **extensor muscles of the forearm.**<br>• Pain and tenderness localised to the lateral epicondyle<br>• Pain worse on resisted wrist extension with the elbow extended or supination of the forearm with the elbow extended<br>• It is a self-limiting condition, episodes typically last between 6 months and 2 years. Patients tend to have acute pain for 6-12 weeks.<br>• Supportive ttt: rest, ice, activity restriction, NSAIDs, Glyceryl trinitrate patches over the painful area and physiotherapy. |
| Medial epicondylitis (golfer's elbow) | **Features**<br>• pain and tenderness localised to the medial epicondyle<br>• pain is aggravated by wrist flexion and pronation<br>• symptoms may be accompanied by numbness / tingling in the 4th and 5th finger due to ulnar nerve involvement |
| Radial tunnel syndrome | Most commonly due to compression of the posterior interosseous branch of the radial nerve. It is thought to be a result of overuse.<br>**Features:**<br>• Symptoms are similar to lateral epicondylitis making it difficult to diagnose<br>• However, the pain tends to be around 4-5 cm distal to the lateral epicondyle<br>• Symptoms may be worsened by extending the elbow and pronating the forearm |

| | |
|---|---|
| **Cubital tunnel syndrome** | Due to the compression of the **ulnar nerve**.<br>**Features**<br>• Initially intermittent tingling in the **4th and 5th finger**<br>• May be worse when the elbow is resting on a firm surface or flexed for extended periods<br>• Later numbness in the 4th and 5th finger with associated weakness |
| **Olecranon bursitis** | Swelling over the posterior aspect of the elbow. There may be associated pain, warmth and erythema. It typically affects middle-aged male patients. |

## De Quervain's tenosynovitis

De Quervain's tenosynovitis is a common condition in which the **sheath** containing the extensor pollicis brevis and abductor pollicis longus tendons is inflamed.

It typically affects **females** aged **30 - 50 years old.**

### Features:

- **Pain on the radial side of the wrist**
- **Tenderness** over the **radial styloid process**
- **Painful abduction** of the thumb against resistance
- **Finkelstein's test**: with the thumb is flexed across the palm of the hand, pain is reproduced by movement of the wrist into flexion and ulnar deviation

### Management:

- Analgesia
- Steroid injection
- Immobilisation with a thumb splint (spica) may be effective
- Surgical treatment is sometimes required

# Dupuytren's contracture

## Definition

- progressive painless contracture of the palmar facial bands, causing flexion deformities of the fingers.
- **autosomal-dominant** condition with variable penetrance.

## Prevalence

- has a **male**: female predominance of 10:1.
- prevalence rates approaching 25% in elderly Scandinavians.
- most commonly observed in persons of Northern European descent and affects 4-6% of Caucasians worldwide.

## Pathophysiology

- **fibroblast proliferation**, and collagen deposition leading to contractures of the palmar fascia.
- **Interleukin 1 (IL-1)** is the most abundant cytokine
- Normal palmar fascia is primarily composed of type I collagen; Dupuytren disease is associated with an **increase in type III collagen**.

## Risk factor:

- **Alcoholism** (10%),
- diabetes mellitus (8%).
- previous myocardial infarction,
- hand trauma,
- HIV infection,
- cigarette smoking.

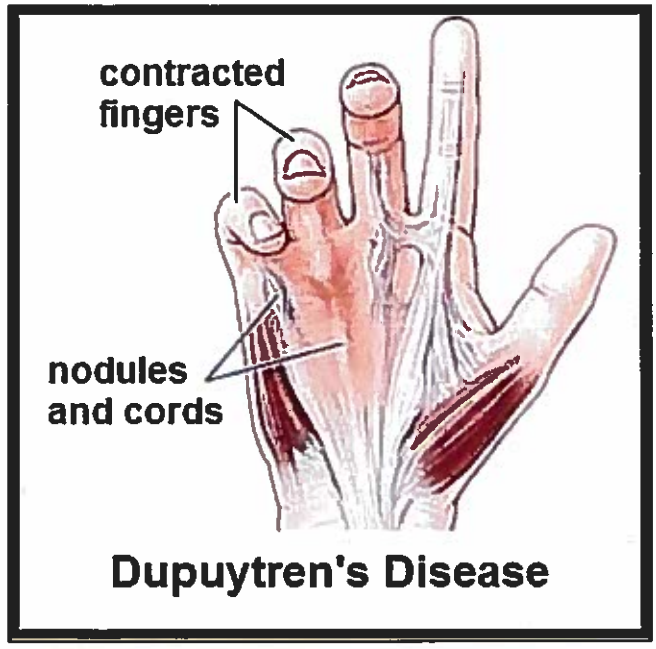
## Features

- bilateral in 45%;
- in unilateral cases, the right side is more often affected.
- The ring finger is most commonly involved, followed by the fifth digit and then the middle finger. The index finger and the thumb are typically spared.
- Penile fibromatosis (Peyronie's disease) is seen in about 7-10% of patients.

**Rheumatoid arthritis seems to protect against the development of Dupuytren disease.**

## Management

- Surgery followed by physiotherapy to improve finger function is the recommended course of action.
- Collagenase therapy may be an alternative to surgery in some cases.




**Ledderhose disease** is involvement of the plantar fascia by a similar process of nodule and cord formation leading to **contraction of the toes.**

# Compartment syndrome

**Pain with passive stretching of the muscles, is the earliest clinical indicator of compartment syndrome.**

- Patients with compartment syndrome typically present with **pain whose severity appears out of proportion to the injury**
- The pain of compartment syndrome is often:
  - described as burning, deep and aching in nature
  - **worsened by passive stretching of the involved muscles.**
  - The patient may describe a tense feeling in the extremity.
- The most important diagnostic physical finding is a firm, wooden feeling on deep palpation.
- **Decreased 2-point discrimination is the most consistent early finding**
- in acute anterior lower leg compartment syndrome, the first sign to develop may be numbness between the first 2 toes (superficial peroneal nerve).
- A **Creatine phosphokinase (CPK)** concentration of 1000-5000 U/mL or greater or the presence of **myoglobinuria** can suggest compartment syndrome.
- **Measurement of intracompartmental pressures** remains the **standard for diagnosis** of compartment syndrome.

## Risk factors

- Trauma
- Anticoagulation therapy and bleeding disorders (eg, hemophilia) significantly increase the likelihood of compartment syndrome.
- Vigorous exertion may lead to compartment syndrome. Compartment syndrome has been found in soldiers and athletes without any trauma.
- If compartment syndrome is suspected, check intracompartmental pressure, even in the absence of any trauma history.

### structures at risk

**Forearm compartments and structures at risk:**

- ventral compartment - median and ulnar nerves; radial and ulnar arteries
- dorsal compartment - posterior interosseous nerve; no major vessels

**Lower limb and structures at risk:**

- anterior tibial compartment - deep peroneal nerve; anterior tibial artery
- superfical posterior compartment - no major nerves or vessels

- deep posterior compartment - posterior tibial nerves and vessels; peroneal artery
- peroneal compartment - deep and superfical peroneal nerves
- Loss of peripheral pulses is a late sign indicating that the pressure within the compartment has exceeded arterial blood pressure.
- Compartment syndrome can occur in the absence of a fracture, for example, crush injuries.
- Pain is the earliest and most reliable symptom of the onset of compartment syndrome.
- **Passive stretch of the muscles traversing the compartment increases pain.**
- Treatment involves decompression of the affected compartment(s) including the skin.

## Feature

High risk injuries are fractures of the forearm and lower leg, especially those that have been internally fixed or infected.

**Early features of an evolving compartment syndrome are:**

- increasing pain despite immobilisation
  - **Passive stretch of affected muscles exacerbates pain**
- sensory deficit in the distribution of the peripheral nerve(s) passing through that compartment
- swelling and tenderness of the muscle compartment
- pain on passive stretching of muscles within the compartment - for example, passive extension of the toes or fingers causing increased pain in the calf or the forearm

**Late features** are those of tissue ischaemia with additionally, pallor, pulselessness, paralysis, coolness and loss of capillary return

## Treatment

- Early orthopaedic referral and continuous instrumented pressure monitoring is necessary.
- **Urgent decompression is required to prevent severe ischaemia.**
- All potentially constricting dressings, casts and splints must be removed
- The compartment pressure should be measured. **Open fasciotomy is indicated if it is above 40 mm Hg**. Otherwise, the limb should be closely observed until improvement is apparent clinically.
- If no improvement occurs, perform a fasciotomy, which in the leg, may mean opening all four compartments.

## Dactylitis

- Dactylitis describes the inflammation of a digit (finger or toe).
- **A 'sausage-shaped' digit is a classical description of dactylitis.**
- Dactylitis is not a feature of rheumatoid arthritis.
- Ex. Pt. with inflamed 2nd metatarsophalangeal joint

### Causes include:

- Spondylarthritis: e.g., Psoriatic and reactive arthritis
- Sickle-cell disease
- Other rare causes include tuberculosis, sarcoidosis and syphilis

## Lower back pain (LBP)

Lower back pain (LBP) is one of the most common presentations seen in practice.

Whilst the majority of presentations will be of a non-specific muscular nature it is worth keeping in mind possible causes which may need specific treatment.

### Red flags for lower back pain:

- Age < 20 years or > 50 years
- History of previous malignancy
- Night pain
- History of trauma
- Systemically unwell e.g. weight loss, fever

The table below indicates some specific causes of LBP:

| | |
|---|---|
| Facet joint | • May be acute or chronic<br>• Pain worse in the morning and on standing<br>• On examination there may be pain over the facets.<br>• The pain is typically worse on extension of the back |
| Spinal stenosis | • Usually gradual onset<br>• Unilateral or bilateral leg pain (with or without back pain), numbness, and weakness which is worse on walking. Resolves when sits down.<br>• Pain may be described as 'aching', 'crawling'.<br>• Relieved by sitting down, leaning forwards and crouching down.<br>• Clinical examination is often normal.<br>• Requires MRI to confirm diagnosis. |
| Ankylosing spondylitis | • Typically a young man who presents with lower back pain and stiffness<br>• Stiffness is usually worse in morning and improves with activity<br>• Peripheral arthritis (25%, more common if female) |
| Peripheral arterial disease | • Pain on walking, relieved by rest<br>• Absent or weak foot pulses and other signs of limb ischaemia<br>• Past history may include smoking and other vascular diseases |

## Lower back pain: prolapsed disc

A prolapsed lumbar disc usually produces clear dermatomal leg pain associated with neurological deficits.

### Features:

- **Leg pain usually worse than back**
- **Pain often worse when sitting**
- **Positive stretch test (femoral / sciatic nerve)**

The table below demonstrates the expected features according to the level of compression:

| Site of compression | Features |
|---|---|
| L3 nerve root compression | Sensory loss over anterior **thigh**<br>Weak quadriceps<br>Reduced knee reflex<br>Positive femoral stretch test |
| L4 nerve root compression | Sensory loss anterior aspect of **knee**<br>Weak quadriceps<br>Reduced knee reflex<br>Positive femoral stretch test |
| L5 nerve root compression | Sensory loss **dorsum of foot**<br>Weakness in foot and big toe **dorsiflexion**<br>Reflexes intact<br>Positive sciatic nerve stretch test |
| S1 nerve root compression | Sensory loss **posterolateral aspect of leg** and **lateral aspect of foot**<br>Weakness in **plantar flexion** of foot<br>Reduced ankle reflex<br>Positive sciatic nerve stretch test |

## Management:

- Similar to that of other musculoskeletal lower back pain: analgesia, physiotherapy, exercises
- if symptoms persist 9e.g. after 4-6 weeks) then referral for consideration of MRI is appropriate

# Hip pain in adults

The table below provides a brief summary of the potential causes of hip pain in adults

| Condition | Features |
|---|---|
| **Osteoarthritis** | Pain exacerbated by exercise and relieved by rest<br>Reduction in internal rotation is often the first sign<br>Age, obesity and previous joint problems are risk factors |
| **Inflammatory arthritis** | Pain in the morning<br>Systemic features<br>Raised inflammatory markers |
| **Referred lumbar spine pain** | Femoral nerve compression may cause referred pain in the hip<br>Femoral nerve stretch test may be positive - lie the patient prone. Extend the hip joint with a straight leg then bend the knee. This stretches the femoral nerve and will cause pain if it is trapped |
| **Greater trochanteric pain syndrome (Trochanteric bursitis)** | Due to repeated movement of the fibroelastic iliotibial band<br>Pain and tenderness over the lateral side of thigh<br>Most common in women aged 50-70 years |
| **Meralgia paraesthetica** | Caused by compression of lateral cutaneous nerve of thigh<br>Typically burning sensation over antero-lateral aspect of thigh |
| **Avascular necrosis** | Symptoms may be of gradual or sudden onset<br>May follow high dose steroid therapy or previous hip fracture of dislocation |
| **Pubic symphysis dysfunction** | Common in pregnancy<br>Ligament laxity increases in response to hormonal changes of pregnancy<br>Pain over the pubic symphysis with radiation to the groins and the medial aspects of the thighs. A waddling gait may be seen |
| **Transient idiopathic osteoporosis** | An uncommon condition sometimes seen in the third trimester of pregnancy<br>Groin pain associated with a limited range of movement in the hip<br>Patients may be unable to weight bear<br>ESR may be elevated |

# Meralgia paraesthetica

Meralgia paraesthetica comes from the Greek words meros for thigh and algos for pain and is often described as a syndrome of paraesthesia or anaesthesia in the distribution of the lateral femoral cutaneous nerve (LFCN). It is an entrapment mononeuropathy of the LFCN, but can also be iatrogenic after a surgical procedure, or result from a neuroma.
Although uncommon, meralgia paraesthetica is not rare and is hence probably underdiagnosed.

## Anatomy

- The LFCN is primarily a sensory nerve, carrying no motor fibres.
- It most commonly originates from the L2/3 segments.
- After passing behind the psoas muscle, it runs beneath the iliac fascia as it crosses the surface of the iliac muscle and eventually exits through or under the lateral aspect of the inguinal ligament.
- As the nerve curves medially and inferiorly around the anterior superior iliac spine (ASIS), it may be subject to repetitive trauma or pressure.
- Compression of this nerve anywhere along its course can lead to the development of meralgia paraesthetica.

## Epidemiology

- The majority of cases occur in people aged between 30 and 40.
- In some, both legs may be affected.
- It is more common in men than women.
- Occurs more commonly in those with diabetes than in the general population.

## Risk factors

- Obesity
- Pregnancy
- Tense ascites
- Trauma
- Iatrogenic, such as pelvic osteotomy, spinal surgeries, laparoscopic hernia repair and bariatric surgery. In some cases, may result from abduction splints used in the management of Perthe's disease.
- Various sports have been implicated, including gymnastics, football, bodybuilding and strenuous exercise.
- Some cases are idiopathic.

Patients typically present with the following symptoms in the upper lateral aspect of the thigh:

- Burning, tingling, coldness, or shooting pain
- Numbness
- Deep muscle ache
- Symptoms are usually aggravated by standing, and relieved by sitting
- They can be mild and resolve spontaneously or may severely restrict the patient for many years.

**Signs:**

- Symptoms may be reproduced by deep palpation just below the ASIS (pelvic compression) and also by extension of the hip.
- There is altered sensation over the upper lateral aspect of the thigh.
- There is no motor weakness.

**Investigations:**

- The pelvic compression test is highly sensitive, and often, meralgia paraesthetica can be diagnosed based on this test alone
- Injection of the nerve with local anaesthetic will abolish the pain. Using ultrasound is effective both for diagnosis and guiding injection therapy in meralgia paraesthetica
- Nerve conduction studies may be useful.

## Baker cyst (popliteal cyst)

It is the most common mass in the popliteal area.

It is the results of synovial fluid distending the gastrocnemio-semimembranosus bursa rather than being a true cyst.

**Causes:** the most common cause >> **osteoarthritis**

**Diagnosis** by knee **US** or if in doubt **MRI** can be considered to confirm the origin of the cyst.

**Complication: rupture or dissection of fluid into the adjacent proximal gastrocnemius** muscle belly which results in **syndrome mimicking the symptoms of a DVT.**

**To differentiate** by using **Doppler US** >>> the vascular lumen is compressible (not compressible in DVT).

While **drainage** may be attempt, **recurrence** is common, and **spontaneous resolution** may itself occur over the course of 1-2 years.

**EX:** Pt presented with a picture **like acute LL DVT, but with normal Duplex US** and he has a history of **previous behind knee swelling** before that >>> **Backer cyst.**

## Ankle injury: Ottawa rules

The Ottawa Rules with for ankle x-rays have a sensitivity approaching 100%. **An ankle x-ray** is required **only if** there is **any pain in the malleolar zone** and **any one of** the following findings:

- **Bony tenderness at the lateral malleolar zone** (from the tip of the lateral malleolus to include the lower 6 cm of posterior border of the fibular)
- **Bony tenderness at the medial malleolar zone** (from the tip of the medial malleolus to the lower 6 cm of the posterior border of the tibia)
- **Inability to walk four weight bearing steps immediately after the injury** and in the emergency department

There are also Ottawa rules available for both foot and knee injuries

## Charcot joint

In patients with **longstanding diabetes** and **peripheral neuropathy**, a **red hot swollen foot** should raise suspicion of Charcot neuroarthropathy.

Diagnosis is suggested by **severe joint destruction** with **minimal symptoms** and **surprisingly normal joint**.

First described in 1868 by Charcot in a patient with syphilis, but also seen in syringomyelia, diabetic neuropathy, spinal cord and peripheral nerve injury, leprosy, multiple sclerosis and meningeomyelocele.

Charcot neuropathy presents as a warm, swollen, erythematous foot and ankle, and infection is important to exclude.

The majority of patients are in their **50-60s**, and they often present in the latter stages of the disease.

It can occur in association with a variety of conditions, including leprosy, poliomyelitis, rheumatoid arthritis, although today **the most common cause is diabetes mellitus.**

The pathophysiology of Charcot neuroarthropathy is not completely understood, but is thought to **start with peripheral neuropathy.**

It is thought to occur due to **increased blood flow** as a result of **neuropathy**, this results in **increased osteoclast activity** and **bone turnover**, the foot is then susceptible to often **very minor trauma** and **destructive changes** take place.

The **lack of pain sensation** may mean that patients subject the foot joints (commonly the **mid-foot at tarsal metatarsal joints**) to **stress injuries** that lead to the **Charcot process**.

It is important to note however that about half of patients present with pain.

**Four stages of Charcot neuropathy are recognised:**

1) **Stage 0 (inflammation):** characterised by erythema and oedema, but no structural changes.
2) **Stage 1 (development):** bone resorption, fragmentation and joint dislocation. Swelling, warmth and erythema persist but there are also radiographic changes such as debris formation at the articular margins, osseous fragmentation and joint disruption.
3) **Stage 2 (coalescence):** bony consolidation, osteosclerosis and fusion are all seen on plain radiographs.
4) **Stage 3 (reconstruction):** osteogenesis, decreased osteosclerosis, and progressive fusion. Healing and new bone formation occur, and the deformity becomes permanent.

**Radiographs** are an important part of investigating a patient with possible Charcot arthropathy. All radiographs should be taken **in the weight-bearing position.**

**MRI** can demonstrate changes in the earlier stages of the condition, and is therefore important in allowing treatment to be instigated earlier.

**Indium-labelled WBCs scan:** although it is not widely available, it is **the best** way to **differentiate** between **infective causes of foot and Charcot's arthropathy.**

In stages 0 and 1 the treatment is **immediate immobilisation** and **avoidance of weight-bearing. A total-contact cast** is worn until the redness, swelling and heat subside (generally 8-12 weeks, changed every 1-2 weeks to minimise skin damage). After this the patient should use a removable brace for a total of 4 to 6 months.

D.D: Osteomyelitis.

## Treatment:

- First line ttt is **total contact plaster and rest for at least 3 months** (immobilisation in a plaster cast for 3-6 months): this allow bone remodelling/repair to occur.
- Bisphosphonates can be used, but evidence of clinical benefit is lacking.
- Surgery is reserved for severe deformities that are susceptible to ulceration, and where braces and orthotic devices are difficult to use.

# Rheumatology disorders

## Osteoarthritis

Osteoarthritis: according to NICE guidelines 2020

### Introduction

- Osteoarthritis refers to a clinical syndrome of joint pain accompanied by varying degrees of functional limitation and reduced quality of life.
- It is the most common form of arthritis, and one of the leading causes of pain and disability worldwide.
- The most commonly affected peripheral joints are the knees, hips and small hand joints.
- Pain, reduced function and effects on a person's ability to carry out their day-to-day activities can be important consequences of osteoarthritis.
- Pain in itself is also a complex biopsychosocial issue, related in part to a person' expectations and self-efficacy. (That is, their belief in their ability to complete tasks and reach goals), and is associated with changes in mood, sleep and coping abilities.
- There is often a poor link between changes visible on an X-ray and symptoms of osteoarthritis: minimal changes can be associated with a lot of pain, or modest structural changes to joints can occur with minimal accompanying symptoms.
- Contrary to popular belief, osteoarthritis is not caused by ageing and does not necessarily deteriorate.
- There are a number of management and treatment options (both pharmacological and non-pharmacological), which this guideline addresses and which represent effective interventions for controlling symptoms and improving function.

### Diagnosis:

- Diagnose osteoarthritis clinically without investigations if a person:
  - is 45 or over and
  - has activity-related joint pain and
  - has either no morning joint-related stiffness or morning stiffness that lasts no longer than 30 minutes.

## Management

NICE published guidelines on the management of osteoarthritis (OA)

- all patients should be offered help with weight loss, given advice about local muscle strengthening exercises and general aerobic fitness
- **paracetamol and topical NSAIDs** are first-line analgesics. Topical NSAIDs are indicated only for OA of the knee or hand
- second-line treatment is oral NSAIDs/COX-2 inhibitors, opioids, capsaicin cream and intra-articular corticosteroids. **A proton pump inhibitor should be co-prescribed with NSAIDs** and COX-2 inhibitors. These drugs should be avoided if the patient takes aspirin
- non-pharmacological treatment options include supports and braces, TENS and shock-absorbing insoles or shoes
- if conservative methods fail then refer for consideration of joint replacement

### What is the role of glucosamine?

- normal constituent of glycosaminoglycans in cartilage and synovial fluid
- a systematic review of several double-blind RCTs of glucosamine in knee osteoarthritis **reported significant short-term symptomatic benefits including significantly reduced joint space narrowing and improved pain scores**
- more recent studies have however been mixed
- NICE guidelines suggest it is not recommended

# Osteoarthritis of the hand

Osteoarthritis (OA) of the hands is sometimes referred to as nodal arthritis. It results from the loss of cartilage at synovial joints and is often accompanied by the degeneration of underlying bone.

## Epidemiology

- There may be a positive family history
- More commonly affects women (M:F 1:3)
- Rare to present before 55 years of age
- Radiologic signs are more common than symptoms
- The presence of hand OA increases the risk of future hip and knee OA (higher for hip OA than for knee OA)

## Risk factors:

- Previous trauma of a joint increases the risk of having OA in that joint
- Obesity
- Hypermobility of a joint increases the risk of OA in that joint

- Occupation e.g., cotton workers and farmers are more susceptible to hand OA
- Osteoporosis reduces the risk of OA

## Features:

- Usually bilateral: Usually one joint at a time is affected over a period of several years. **The carpometacarpal joints (CMCs), distal interphalangeal joints (DIPJs)** are affected more than the proximal interphalangeal joints (PIPJs).
- Episodic joint pain: An intermittent ache. Provoked by movement and relieved by resting the joint.
- Stiffness
  - worse after long periods of inactivity e.g. waking up in the morning
  - stiffness lasts only a few minutes compared to the morning joint stiffness seen in rheumatoid arthritis.
- Painless nodes (bony swellings)
  - Heberden's nodes at the DIP joints
  - Bouchard's Nodes at the PIP joints
  - these nodes are the result of osteophyte formation.
- Squaring of the thumbs: Deformity of the carpometacarpal joint of the thumb resulting in fixed adduction of the thumb.
- Functionally patients do not usually have any problems. If there is severe involvement of the DIPJs, there may be reduced grip strength which can result in disuse atrophy.

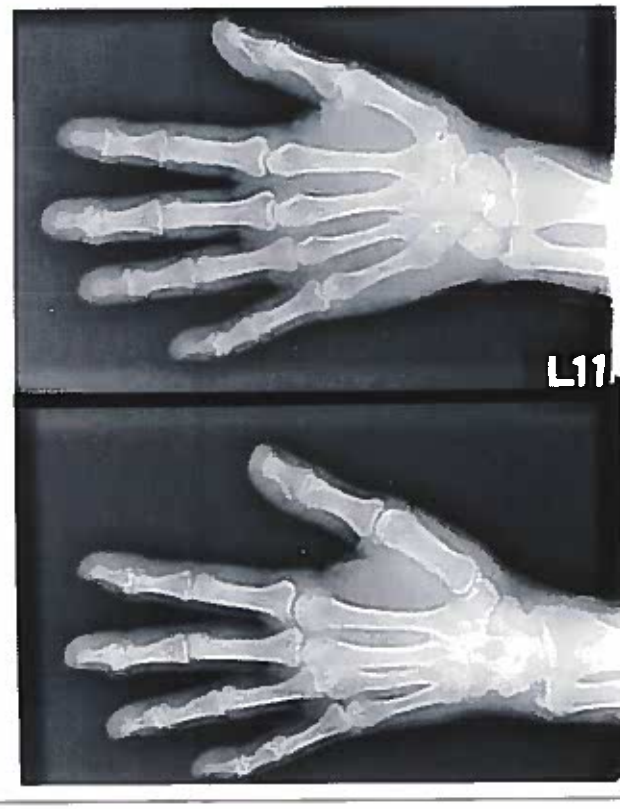
## Investigations:

- X-ray: radiologically there are osteophytes and joint space narrowing. Often signs may be visible on X-ray, before symptoms develop

Osteoarthritis in an elderly woman with Heberden nodes at the distal interphalangeal joints. T here is some swelling beginning at the proximal interphalangeal joints creating Bouchard nodes.

Osteoarthritis with visible Heberden (D IP) and Bouchard (PIP) nodes.

Osteoarthritis with visible unilateral knee effusion. The effusion was tapped and the synovial fluid was consistent with osteoarthritis. A n intraarticular steroid injection was given and provided great relief to the pain and stiffness.




Joint space narrowing, marginal osteophytes, and Heberden nodes at the distal interphalangeal joints of the second through fifth fingers.

Osteoarthritis of the knee causing joint space narrowing, sclerosis, and bony spurring in all three compartments of the right knee, most pronounced in the medial compartment

Articular space narrowing, sclerosis, and subchondral cyst formation of both hips because of osteoarthritis.

## Management:

### Non-pharmacological management

- Advise people with osteoarthritis to exercise as a core treatment **irrespective of age, comorbidity, pain severity or disability. Exercise should include:**
- local muscle strengthening and
- general aerobic fitness.

Exercise has been found to be beneficial but the clinician needs to make a judgement in each case on how to effectively ensure participation. supports and braces, topical capsaicin, Application of heat or cold packs, TENS

(Transcutaneous electrical nerve stimulation) and shock absorbing in soles or shoes can be used

## Referral for consideration of joint surgery

- Base decisions on referral thresholds on discussions between patient representatives, referring clinicians and surgeons, rather than using scoring tools for prioritisation.
- Refer for consideration of joint surgery before there is prolonged and established functional limitation and severe pain.

**PHARMACOLOGICAL MANAGEMENT:**

1) **paracetamol: regular doses.**
2) **NSAIDs and highly selective COX-2 inhibitors**

- Although NSAIDs and COX-2 inhibitors may be regarded as a single drug class of 'NSAIDs', these recommendations use the two terms for clarity and because of the differences in side-effect profile.
- Where paracetamol or topical NSAIDs are ineffective for pain relief for people with osteoarthritis, then substitution with an oral NSAID/COX-2 inhibitor should be considered.
- Where paracetamol or topical NSAIDs provide insufficient pain relief for people with osteoarthritis.
- Use oral NSAIDs/COX-2 inhibitors at the lowest effective dose for the shortest possible period of time.
- When offering treatment with an oral NSAID/COX-2 inhibitor, the first choice
- should be either a standard NSAID or a COX-2 inhibitor (other than etoricoxib 60 mg).
- In either case, co-prescribe with a proton pump inhibitor (PPI), All oral NSAIDs/COX-2 inhibitors have analgesic effects of a similar magnitude but vary in their potential gastrointestinal, liver and cardio-renal toxicity.
- Intra-articular injections
- Intra-articular corticosteroid injections should be considered as an adjunct to core treatments for the relief of moderate to severe pain in people with osteoarthritis.

The **trapeziometacarpal joint (first carpometacarpal joint) (base of thumb)** is the most **common** site of **hand** osteoarthritis especially in **postmenopausal** women.

**NB:** Treatments which are not recommended by NICE include rubefacients, intra-articular hyaluronic, electro-acupuncture and chondroitin or glucosamine products.

# Rheumatoid arthritis (RA)

**Please refer to NICE guidelines 2020**

## Quality statements

**Statement 1** Adults with suspected persistent synovitis affecting more than 1 joint, or the small joints of the hands and feet, are referred to rheumatology services within 3 working days of presenting in primary care. [2013, updated 2020]

**Statement 2** Adults with active rheumatoid arthritis start conventional disease modifying anti-rheumatic drug (cDMARD) monotherapy within 6 weeks of referral, with monthly monitoring until their treatment target is met. [2013, updated 2020]

**Statement 3** Adults with rheumatoid arthritis are given opportunities throughout the course of their disease to take part in educational activities that support self-management. [2013, updated 2020]

**Statement 4** Adults with rheumatoid arthritis and disease flares or possible treatment-related side
effects receive advice within 1 working day of contacting rheumatology services. [2013, updated 2020]

**Statement 5** Adults with rheumatoid arthritis have a comprehensive annual review that is coordinated by rheumatology services. [2013, updated 2020]

**Epidemiology:**

- **Prevalence** in 1% of UK population {1000 from100,000 – 200 from 20000}.
- **The incidence of rheumatoid arthritis is approximately 2.5 per 10 000 per year (1.5 in men and 3.6 in women).**
  - **Peak onset** = 30-50 years, although occurs in all age groups
  - F:M ratio = 3:1
  - Some ethnic differences e.g. **high in Native Americans**
  - Associated with **HLA-DR4** (especially **Felty's syndrome**).
  - RA is associated with several antibodies such as RF, collagen antibody, capable of reaction **at sites other than the joints** (i.e. the disease is not confined to the joints).
  - Damage is mediated by several means, including **macrophages** activated by **CD4+ T cells**, and by complement fixing immune complexes.

### Rheumatoid arthritis - TNF is key in pathophysiology

A number of studies have suggested a link between **Proteus mirabilis** infection and the development of **RA** in susceptible individuals, and this may contribute to the increased incidence of RA in **women**, who are more susceptible to **UTI**.

## Diagnosis

### Persistent synovitis

- Signs and symptoms of persistent synovitis include persistent **(not resolving within 3 to 4 weeks)** pain, swelling, heat, early morning stiffness lasting more than 30 minutes and often recurring after longer periods of rest, and loss of function of the affected joint.
- Occasionally the joints may also be red, but this is unusual.
- The person may also have systemic symptoms of inflammation, which may include malaise, fever, sweats, fatigue and weight loss.

**NICE** have stated that **clinical diagnosis** is more important than **criteria** such as those defined by the American College of Rheumatology.

**The most commonly used classification criteria are the American College of Rheumatology criteria. These criteria do not perform well in early disease.**

**Rheumatoid arthritis is a clinical diagnosis.**

**The classic features are:**

- **Symmetrical inflammatory polyarthritis**
- Arthritis affecting the **small** joints of the **hands and feet.**

**AULAR (Europian league against rheumatology) criteria for diagnosing Rh. Arthritis approved by NICE.**

Classification criteria for rheumatoid arthritis (add score of categories A-D; a score of 6/10 is needed definite rheumatoid arthritis)

| | | |
|---|---|---|
| **A. Joint involvement** | | |
| | 1 large joint | 0 |
| | 2 - 10 large joints | 1 |
| | 1 - 3 small joints (with or without involvement of large joints) | 2 |
| | 4 - 10 small joints (with or without involvement of large joints) | 3 |
| | 10 joints (at least 1 small joint) | 5 |
| **B. Serology** (at least 1 test result is needed for classification) | | |
| | Negative RF and negative ACPA | 0 |
| | Low-positive RF or low-positive ACPA | 2 |
| | High-positive RF or high-positive ACPA | 3 |
| **C. Acute-phase reactants** (at least 1 test result is needed for classification) | | |
| | Normal CRP and normal ESR | 0 |
| | Abnormal CRP or abnormal ESR | 1 |
| **D. Duration of symptoms** | | |
| | < 6 weeks | 0 |
| | > 6 weeks | 1 |

**Key:**

- RF = rheumatoid factor
- ACPA = anti-cyclic citrullinated peptide antibod

## Investigations

### Diagnostic tests are:

### Investigations for diagnosis

- Offer to carry out a blood test for rheumatoid factor in adults with suspected rheumatoid arthritis (RA) who are found to have synovitis on clinical examination.
- Consider measuring anti-CCP antibodies in adults with suspected RA if they are negative for rheumatoid factor.
- X-ray the hands and feet in adults with suspected RA and persistent synovitis.

## MORE DETAILS ABOUT THE ANTIBODIES

**Rheumatoid factor (RF) is a circulating antibody (usually IgM) that reacts with the Fc portion of the patients own IgG**.. It is recommended as the first-line antibody test for patients with suspected rheumatoid arthritis.

### RF can be detected by either

- Rose-Waaler test: sheep red cell agglutination
- Latex agglutination test (less specific)

RF is positive in 70-80% of patients with rheumatoid arthritis, high titre levels are associated with severe progressive disease (but NOT a marker of disease activity.

### Other conditions associated with a positive RF include:

- Felty's syndrome (around 100%)
- Sjogren's syndrome (around 50%)
- infective endocarditis (around 50%)
- SLE (= 20-30%)
- systemic sclerosis (= 30%)
- general population (= 5%)
- rarely: TB, HBV, EBV, leprosy

### Anti-cyclic citrullinated peptide antibody

Anti-cyclic citrullinated peptide antibody may be detectable up to 10 years before the development of rheumatoid arthritis. It has a key role in the diagnosis of rheumatoid arthritis, allowing early detection of patients suitable for aggressive anti-TNF therapy. It has a sensitivity similar to rheumatoid factor (around 70%) with a much higher specificity of 90-95%.

## Rheumatoid arthritis: x-ray changes

### Early x-ray findings:

- **Periarticular (juxta-articular) osteopenia and osteoporosis**
- **Periarticular decalcification**
- loss of joint space
- soft-tissue swelling

### Late x-ray findings:

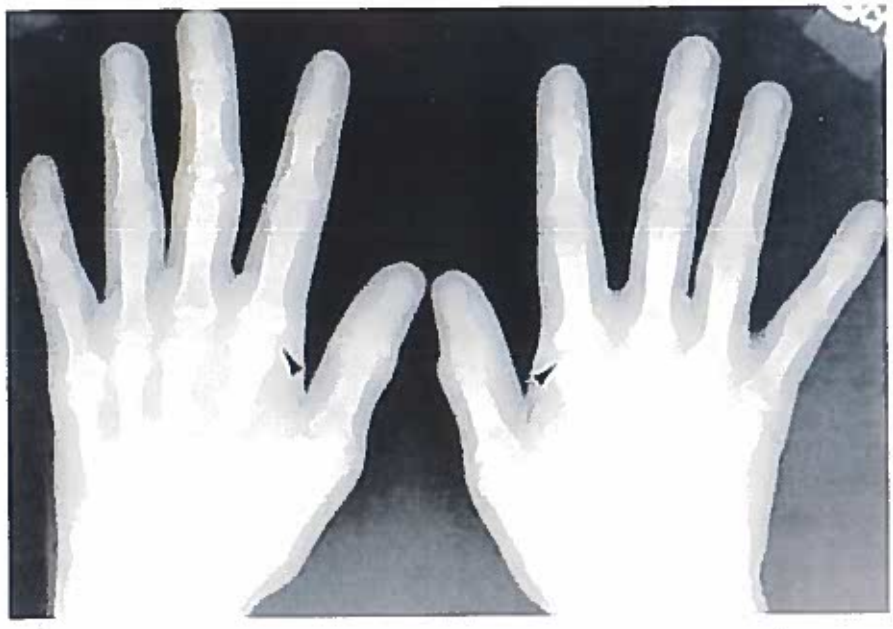
- Periarticular **erosions**
- Subluxation

Rheumatoid arthritis showing typical ulnar deviation at the metacarpophalangeal joints

Rheumatoid arthritis involving the whole upper-extremity joints with nodules on the elbow, wrist, and hand joints.

Rheumatoid arthritis with rheumatoid nodules over the PIP joints along with deformities of the digits.

Rheumatoid arthritis showing ulnar deviation of the fingers at the metacarpophalangeal joints



Hand radiographs in long-standing rheumatoid arthritis demonstrating carpal destruction, radiocarpal joint narrowing, bony erosion, and soft-tissue swelling

Severe changes of late rheumatoid arthritis including radiocarpal joint destruction, ulnar deviation, erosion of the ulnar styloid bilaterally, dislocation of the left thumb proximal interphalangeal (PIP) joint, and dislocation of the right fourth and fifth metacarpophalangeal (MC P) joints.

Dupuytren contracture in a 60-year-old man showing a flexion contracture of the fifth digit and a palmar cord.

* Periarticular osteopenia and osteoporosis would point towards a diagnosis of (RA).
* Loss of joint space is common in both RA and OA also in Pseudogout.
In the **early stages of an insidious onset** of the RA disease, the acute phase markers CRP and ESR are often normal, particularly when small joints are involved.

At this stage of early RA >>> the diagnostically most informative test is **hand and feet X-ray >>> periarticular osteopenia** and **marginal erosions** at affected joints.
**Foot** joints are often radiologically affected **before** hand joints.

## Rheumatoid arthritis: prognostic features

**Poor** prognostic features:

- **Rheumatoid factor** positive
- **Anti-CCP** antibodies
- **HLA DR4**
- **Insidious onset**
- Poor functional status at presentation
- **X-ray: early** articular **erosions** (e.g. **within the first 6 months of presentation** and in less than < 2 years).
- Extra articular features e.g. **nodules**
- **Female** sex.

**NB:** (Acute or Sudden onset is not a poor prognosis)

# Rheumatoid arthritis: management

**EULAR (European league against rheumatology GUIDELINES 2020**

## Initial pharmacological management

- Offer first-line treatment with cDMARD monotherapy using oral methotrexate, leflunomide or sulfasalazine as soon as possible and ideally within 3 months of onset of persistent symptoms.
- Consider hydroxychloroquine for first-line treatment as an alternative to oral methotrexate, leflunomide or sulfasalazine for mild or palindromic disease.
- Escalate dose as tolerated. [2018].

Patients with evidence of joint inflammation should start a **combination** of disease-modifying drugs (**DMARD**) as soon as possible.

**Other important treatment options include analgesia, physiotherapy and surgery.**

- Offer additional cDMARDs (oral methotrexate, leflunomide, sulfasalazine or hydroxychloroquine) in combination in a step-up strategy when the treatment target (remission or low disease activity) has not been achieved despite dose escalation.
- Consider short-term bridging treatment with glucocorticoids (oral, intramuscular or intra-articular) when starting a new cDMARD because of their slow onset of action , usually steroids are needed for 2-3 months till cDMARD are in action. [2018]
- In the balance of its clinical benefits and cost effectiveness, anakinra (IL-1 receptor antagonist) is not recommended for the treatment of RA,

**DMARDs:**

- **Methotrexate** is the most widely used DMARD, usual dose is 7.5-10 mg weekly.
- **Sulfasalazine** (500 mg tab)
- **Leflunomide** (Arava® 20 mg tab)
- **Hydroxychloroquine** (HCQ) (plaquenil® 200 mg tab): less effective.
- Evidence showed that starting treatment with more than 1 conventional DMARD (cDMARD) was no more effective than starting with a single cDMARD.
- The committee agreed that cDMARD monotherapy might have fewer side effects and recommended cDMARD monotherapy as first-line treatment.
- This differed from the 2009 guideline which recommended combination therapy. The difference is largely a result of inclusion of different evidence and a different approach to analysing that evidence.

**TNF-inhibitors (Biologic therapy):**

- The current indication for a TNF-inhibitor is an **inadequate response to at least two DMARDs including methotrexate**
- Adverse effects of TNF blockers include **reactivation of latent tuberculosis** and **demyelination.**
- The risk of TB reactivation is most pronounced in the **first 3 months** of Treatment.
- The current British Thoracic Society BTS guidelines therefore recommend a clinical examination, chest radiograph and thorough history taken to check for prior TB.
- In the UK, patients have a **baseline CXR** and **assessment of risk of infection** with Mycobacterium tuberculosis prior to starting treatment with anti-TNF α.
- Any patient with an abnormal chest radiograph or previous history of TB should be referred for assessment by a specialist with an interest in TB.
- Those with symptoms raising a suspicion of TB should be thoroughly investigated to exclude active disease.
- Any patient with active TB, either pulmonary or non-pulmonary, should receive standard chemotherapy. They must **complete 2 months full treatment before starting anti-TNF alpha treatment.**
- Patients with an abnormal chest radiograph consistent with past TB, or a history or prior extra pulmonary TB but who have received previous adequate therapy can be started on anti-TNF alpha therapy but need to be monitored regularly.
- Where there is an abnormal chest radiograph, or a history of prior pulmonary or extra pulmonary TB not previously adequately treated, **chemoprophylaxis with isoniazid for 6 months** should be given before commencing anti-TNF alpha treatment.
- The BTS guidelines have not been updated to include recommendations regarding **Quantiferon Gold test** and Elispot tests. Practice does vary between individual NHS trusts regarding who to test with one of these, and which to use. However, **the most accepted recommendations are that patients who test positive** with either of these should be **treated with chemoprophylaxis** (either **isoniazid for 6 months, or dual therapy Rifampicin + INH for 2 months) at the same time** as being **started on anti-TNF alpha treatment.**
- For patients with a normal chest radiograph who have not started immunosuppressive therapy, **a tuberculin test is helpful.**

TNF-inhibitors should be stopped **2-4 weeks before any major operation.**
Stopping earlier may lead to disease flare and thus interfere with the surgery.
Treatment may be restarted postoperatively if there is no evidence of infection.

- Examples of anti-TNF alpha agents:
  - Etanercept,
  - Infliximab,
  - Adalimumab,
- **Etanercept SC:**
  - It is a recombinant human protein, acts as a decoy receptor for TNF-α, it is a fusion protein that mimics the inhibitory effects of naturally occurring soluble TNF receptors.
  - **Dose: 25 mg SC** administration **twice weekly,**
  - It can cause demyelination and risks of TB reactivation.
  - It can be used alone in the treatment of RA or with methotrexate.
  - Also, can be used in psoriasis and psoriatic arthritis.
  - Used with caution in patients with asthma, renal impairment.
- **Infliximab IV:**
  - Monoclonal antibody, binds to TNF-α and prevents it from binding with TNF receptors, **IV** administration, risks include reactivation of tuberculosis
  - Infliximab should normally be used in combination with methotrexate and requires IV infusion in a hospital setting.
  - If a patient is intolerant of methotrexate, etanercept (anti-TNF receptor antibody) and adalimumab (humanised anti-TNF antibody) are alternatives to infliximab which can be given as monotherapy.
  - **Infliximab** is also used in **active Crohn's** disease **unresponsive to steroids.**
- **Adalimumab**: monoclonal antibody, SC administration

**Tocilizumab**: (anti-IL 6 receptor).

**Rituximab:**

- **Anti-CD20** monoclonal antibody, results in **B-cell depletion.**
- **Two 1g intravenous infusions are given two weeks apart.**
- The most common side effects:
  - **Allergic reactions:** low BP and facial flushing during IV infusion.
  - Flu-like symptoms: **high fever, chills,** weakness, muscle aches, tiredness, dizziness and headache during IV infusion.
  - Nausea and vomiting.
  - Tumour pain.
- Uses: Non-Hodgkin lymphoma, Pure red cell aplasia, ITP, Evans syndrome, Rheumatoid arthritis, Multiple sclerosis, SLE, Vasculitis.

**Abatacept:**

- Cytotoxic T-lymphocyte antigen 4 **(CTLA 4) homologue.**

- Fusion protein that modulates a key signal required for activation of T lymphocytes
- Leads to decreased T-cell proliferation and cytokine production
- Given as an infusion
- Not currently recommend by NICE

### Monitoring response to treatment

- NICE recommends using a combination of CRP and disease activity (using a composite score such as DAS28) to assess response to treatment.

### Flares

- flares of RA are often managed with corticosteroids - oral or intramuscular

## Symptom control

- **Consider oral non-steroidal anti-inflammatory drugs (NSAIDs, including traditional NSAIDs and cox II selective inhibitors),** when control of pain or stiffness is inadequate.
- Take account of potential gastrointestinal, liver and cardio-renal toxicity, and the person's risk factors, including age and pregnancy.
- **When treating symptoms of RA with oral NSAIDs:**
  - offer the lowest effective dose for the shortest possible time
  - offer a proton pump inhibitor (PPI), and review risk factors for adverse events regularly. If a person with RA needs to take low-dose aspirin, healthcare professionals should consider other treatments before adding an NSAID (with a PPI) if pain relief is ineffective or insufficient. [2009, amended 2018]

## Non-pharmacological management

### Physiotherapy

Adults with RA should have access to specialist physiotherapy, with periodic review to:

- improve general fitness and encourage regular exercise.
- learn exercises for enhancing joint flexibility, muscle strength and managing other functional impairments.
- learn about the short-term pain relief provided by methods such as transcutaneous electrical nerve stimulators (TENS) and wax baths. [2009]

### Occupational therapy

**Adults with RA should have access to specialist occupational therapy, with periodic review, if they have:**

- difficulties with any of their everyday activities, or
- problems with hand function.

**Hand exercise programmes**

**Consider a tailored strengthening and stretching hand exercise programme for adults with RA with pain and dysfunction of the hands or wrists if:**

- they are not on a drug regimen for RA, or
- they have been on a stable drug regimen for RA for at least 3 months.

The tailored hand exercise programme for adults with RA should be delivered by a practitioner with training and skills in this area.

**Podiatry**

All adults with RA and foot problems should have access to a podiatrist for assessment and periodic review of their foot health needs. Functional insoles and therapeutic footwear should be available for all adults with RA if indicated.

**Psychological interventions**

- Offer psychological interventions (for example, relaxation, stress management
- and cognitive coping skills [such as managing negative thinking]) to help adults with RA adjust to living with their condition.

NICE has published a guideline on depression in adults with a chronic physical health problem.

**Diet and complementary therapies**

- Inform adults with RA who wish to experiment with their diet that there is no strong evidence that their arthritis will benefit.
- However, they could be encouraged to follow the principles of a Mediterranean diet (more bread, fruit, vegetables and fish; less meat; and replace butter and cheese with products based on vegetable and plant oils.
- Inform adults with RA who wish to try complementary therapies that although some may provide short-term symptomatic benefit, there is little or no evidence for their long-term efficacy.
- If an adult with RA decides to try complementary therapies, advise them:
  - these approaches should not replace conventional treatment
  - this should not prejudice the attitudes of members of the multidisciplinary team, or affect the care offered.

**Monitoring**

- Ensure that all adults with RA have:
  - rapid access to specialist care for flares
  - information about when and how to access specialist care, and ongoing drug monitoring. [2018]

- Consider a review appointment to take place 6 months after achieving treatment target (remission or low disease activity) to ensure that the target has been maintained. [2018]
- **Offer all adults with RA, including those who have achieved the treatment target, an annual review to:**
  - assess disease activity and damage, and measure functional ability. (using, for example, the Health Assessment Questionnaire [HAQ])
  - check for the development of comorbidities, such as hypertension, ischaemic heart disease, osteoporosis and depression.
  - assess symptoms that suggest complications, such as vasculitis and disease of the cervical spine, lung or eyes.
  - organise appropriate cross referral within the multidisciplinary team
  - assess the need for referral for surgery .
  - assess the effect the disease is having on a person's life.
  - For adults who have maintained the treatment target (remission or low disease activity) for at least 1 year without glucocorticoids, consider cautiously reducing drug doses or stopping drugs in a step-down strategy. Return promptly to the previous DMARD regimen if the treatment target is no longer met. [2018]

**Timing and referral for surgery:**

- Offer to refer adults with RA for an early specialist surgical opinion if any of the following do not respond to optimal non-surgical management:
- persistent pain due to joint damage or other identifiable soft tissue cause
- worsening joint function
- progressive deformity
- persistent localised synovitis. [2009]

**Offer to refer adults with any of the following complications for a specialist surgical opinion before damage or deformity becomes irreversible:**

- imminent or actual tendon rupture
- nerve compression (for example, carpal tunnel syndrome)
- stress fracture.

## Rheumatoid arthritis: complications

A wide variety of extra-articular complications occur in patients with RA:

- **Cardiac:**
  - **IHD**: RA carries a similar risk to T2DM,
  - **Constrictive pericarditis** (in **30%**)

- **Respiratory:**
  - Pulmonary **fibrosis (Fibrosing alveolitis) >> progressive breathlessness,**
  - Pleural effusion,
  - Pulmonary nodules,
  - **Bronchiolitis obliterans,**
  - Methotrexate pneumonitis (it is potentially life-threatening and occurs in 1-5% of patients who are treated with methotrexate,
  - Pleurisy,
  - Caplan's syndrome (RA + massive fibrotic **nodules** with **pneumoconiosis** occupational coal dust exposure).
- **Ocular** (it is common and occur in 25% of patients):
  - **keratoconjunctivitis sicca (most common)**: (dry, burning and gritty eyes caused by decreased tear production)
  - **Episcleritis (erythema only)**
  - **Scleritis (erythema and pain)**
  - Corneal ulceration (**Corneal melts** = perforated corneal ulceration).
  - Keratitis,
  - Steroid-induced cataracts,
  - Chloroquine retinopathy
- Osteoporosis
- Increased risk of infections (possibly atypical): **CMV-associated colitis.**
- Depression
- Skeletal: **carpal tunnel syndrome (CTS):** paraesthesia in hands that may let him awake from sleep

**Less common complications of RA:**

- **Felty's syndrome** (**Active RA + splenomegaly + low white cell count**).
- **Amyloidosis >>> Renal failure (Nephrotic range proteinuria) >>> high levels of serum amyloid A protein** which is also an acute phase reactant, the kidneys are usually normal size, or slightly large and **hepatomegaly.**
- **AIHA** (autoimmune haemolytic anaemia): **warm** type, **+ve DGT** (direct globulin test) (Coomb's test), spherocytosis, ↑RTX & ↑ LDH. (see Haematology).

- **Rheumatoid arthritis: patients have an increased risk of IHD**

**Episcleritis is not painful, Scleritis is painful**

Proteus mirabilis is a Gm –ve rod, causing **UTI** >>> predispose susceptible pt. to **RA**

# Rheumatoid arthritis: summary of drug side-effects

The table below lists some of the characteristic (if not common) side-effects of drugs used to treat rheumatoid arthritis:

**Cessation of the drug is the only effective management of the toxicity.**

| Drug | Side-effects |
|---|---|
| Methotrexate | Myelosuppression<br>Liver cirrhosis<br>Pneumonitis |
| Sulfasalazine | Rashes<br>Oligospermia<br>Heinz body anaemia<br>Interstitial lung disease |
| Leflunomide | Liver impairment<br>Interstitial lung disease<br>Hypertension |
| Hydroxychloroquine | Retinopathy<br>Corneal deposits |
| Prednisolone | Cushingoid features<br>Osteoporosis<br>Impaired glucose tolerance<br>Hypertension<br>Cataracts |
| Gold | Proteinuria |
| Penicillamine | Proteinuria<br>Exacerbation of myasthenia gravis |
| Etanercept | Demyelination<br>Reactivation of tuberculosis |
| Infliximab | Reactivation of tuberculosis |
| Adalimumab | Reactivation of tuberculosis |
| Rituximab | Infusion reactions are common |
| NSAIDs (e.g., naproxen, ibuprofen) | Bronchospasm in asthmatics<br>Dyspepsia/peptic ulceration |

# Rheumatoid arthritis: pregnancy

**In Pregnancy:**

- **Methotrexate (teratogenic) and NSAIDs (1st trimester, risk of abortion) so they are absolutely contraindicated.**
- **Prednisolone, Sulfasalazine** and **hydroxychloroquine** are safe in pregnancy if these are necessary for treatment of the mother's disease.
- **Sulfasalazine** can be safely used prior to and during all stages of pregnancy, it is compatible with breast feeding, although should be advised with cautions because of the rare possibility that the mother is a slow acylator.
- **Azathioprine** can be used in pregnancy if Sulfasalazine and hydroxychloroquine are not controlling.
- Prednisolone and hydroxychloroquine may be taken whilst breast-feeding.
- Azathioprine, cyclophosphamide, methotrexate and cyclosporine are contraindicated in breast-feeding mothers.

**Azathioprine** can be used during pregnancy **if the benefits outweigh the risks**. Azathioprine can be continued at **the same dose**.
No apparent congenital malformations are known with doses up to 2mg/kg/day.
**During pregnancy >>> continue current dose of azathioprine** and **add folic acid**.
Breast feeding is not recommended with azathioprine.

**Corticosteroids**, the main alternative to azathioprine, are considered **relatively safe** in pregnancy when used in **low dose < 20 mg daily**.
However they may increase the **maternal risk** of HTN, oedema, gestational diabetes, osteoporosis, premature rupture of membranes (PROM), small-for-gestational-age babies (SGA), and increase in risk of cleft palate in foetus of first trimester.
The **lowest possible steroid dose** needed to control activity should be used in pregnancy if the choice is to follow this ttt option.
The routine use of **oral calcium and Vit D** is recommended.
**Stress doses of steroids** should be used **during labour and delivery** if the mother received steroids (even low dose) for more than 2-3 weeks during pregnancy, and the **neonate** should be **monitored** for evidence of adrenal insufficiency and infection.

# Sjogren's syndrome

- Sjogren's syndrome is an **autoimmune** disorder affecting **exocrine** glands resulting in dry mucosal surfaces.
- It may be either:
  - **Primary Sjögren's syndrome (PSS)** or
  - **Secondary to** RA, SLE or other connective tissue disorders, where **it usually develops around 10 years after the initial onset.**
- Sjögren's syndrome is much more common in **females** (**ratio 9:1**).
- There is a marked increased risk of **lymphoid malignancy (NHL) (40-60 folds).**

## Features:

- **Dry eyes:** keratoconjunctivitis sicca
- **Dry skin.**
- **Dry mouth**
- **Dry vagina**
- **Arthralgia**
- **Raynaud's,** myalgia
- **Sensory polyneuropathy**
- **Renal tubular acidosis** (usually **subclinical)**
- **Plasma cell infiltration of salivary and lacrimal glands: Parotid swelling.**

## Investigation:

- **RF** positive in nearly **100%** of patients
- **ANA** positive in **70%**
- **Anti-Ro** (SSA) antibodies in **70%** of patients with PSS
- **Anti-La** (SSB) antibodies in 30% of patients with PSS
- **Hypergammaglobulinemia (↑ IgG)** in **80%**
- **Low C4**
- **Schirmer's test**: filter paper near conjunctival sac to measure tear formation (wetting of **less than 5 mm in 5 minutes** indicates defective tear production).
- **Rose Bengal staining of the eyes** commonly shows punctuate or filamentary keratitis.
- Histology: **focal lymphocytic infiltration >> ↑ risk of lymphoid malignancy**
- **the most definitive test for Sjögren's syndrome >> Labial gland biopsy.**

In RA, RF is positive in 80% of patients, whereas in Sjogren's syndrome and cryoglobulinaemia, it is prevalent in up to 90% of cases.

**Management:**

- Artificial tears.
- Saliva replacement solution
- Vaginal lubricant.
- **Pilocarpine** may stimulate saliva production.

**Complication**

**higher risk of developing lymphoma**

- These lymphomas are primarily of B cell origin.
- High risk factors for lymphoma development in Sjogren's syndrome patients include:
  - persistent unilateral or bilateral parotid gland enlargement,
  - splenomegaly and lymphadenopathy,
  - low C4 complement levels,
  - type 2 mixed cryoglobulinaemia

## Felty's syndrome

It is usually occurs in patients with **long-standing seropositive RA.**

Two third of the patients are **female** (60-70% female predominance).

It is usually recognised from the 5th decade onwards in patients who have had RA for an average of 10 years or more.

C/P: **Active RA** + **Leukopenia** + **Lymphadenopathy** + **Splenomegaly** + also **leg ulcers**, **recurrent infections (URTI)** and **Episcleritis** may be present.

**ANA is positive in more than 90%** of patients with Felty's syndrome.

**Treatment:**

- **Pulsed corticosteroid and/or cyclophosphamide therapy** may be effective in raising neutrophils count,
- **G-CSF** to stimulate the production of granulocytes,
- **Splenectomy** (if failed to respond to medical ttt).

**NB: Active RA** on methotrexate with **leukopenia >>>? Methotrexate-induced** or **Felty's syndrome (+ve ANA)**.

**EX:** Female 66 years old, long history of RA on methotrexate, she has worsening rheumatoid nodules, dry eyes, splenomegaly, pancytopenia TLC 3.5, Hb 9.5, PLT 100 >>> **Felty's** syndrome >>> 1st Treatment is **pulse corticosteroid** (NOT hold methotrexate).
Cyclophosphamide causes **premature ovarian failure** and **infertility** in **both** men and women.
The risk increases with increasing doses of cyclophosphamide and is greater in **younger patients**.
Cyclophosphamide treatment does **not** lead to breast cancer, hyperthyroidism, ovarian cancer, or venous thromboembolism.

# Juvenile idiopathic arthritis (JIA)

## Definition

- The ACR criteria define juvenile rheumatoid arthritis (JRA) by age limit (< 16 y) and the duration of disease (> 6 weeks).

## Epidemiology

- the most common form of arthritis in children and adolescents.
- Prevalence: 1/1000 children
- Sex: ♀ > ♂

## Types

### Oligoarticular JIA

- Most common form (accounts for 50% of all JIA cases)
- affects **four joints or fewer** during the **first 6 months**,
- has the highest risk of developing Chronic anterior uveitis (up to 25%)
  - Bilateral eye involvement is common
- RF negative
- ANA positive (~ 70% of cases)
- Treatment
  - NSAIDs
  - Possibly intra-articular steroid injections
  - Possibly methotrexate

### Polyarticular JIA

- 40% of cases
- characterised by inflammatory arthritis affecting **five or more joints** during the first **6 months** of the disease.
- RF negative
- ANA positive (~ 40% of cases)
- Treatment: Standard therapy with methotrexate and NSAID

### Systemic-onset JIA (Still's disease)

- < 10% of cases
- presents with **fever, arthritis and at least one of the following:**
  - erythematous rash,
  - generalised lymphadenopathy,
  - Hepatosplenomegaly
  - serositis (including pleural and pericardial effusions)
- RF negative
- ↑ Acute phase reactants (e.g., CRP, ferritin)
- Treatment: Poor response to methotrexate and TNF inhibitors (etanercept, adalimumab)

## Risk factors

- **Exposure to antibiotics during childhood may increase the risk of JIA.**

## Features

**Joint pain, daily spiking fevers, and a 'salmon-pink' rash are classic symptoms.**

- persistent non-tender joint **swelling** >> (The cardinal feature)
  - The first manifestation of JIA is often **limping**, especially in young children.
  - The persistent swelling most often occurs in the large joints.
  - Damage to joints is associated with a $T_H1$ response.
- Up to 25% of patients have a **positive anti-nuclear antibody**.
- microcytic anaemia which tends to be resistant to iron replacement
- pericarditis is often found.
- hepatosplenomegaly,
- JIA can decrease bone mass and increase the risk of osteoporosis.
- ↑ ESR (usually seen with all forms of JIA).
- Rheumatoid nodules and rheumatoid factor are usually **absent**
  - Rheumatoid factor (RF) is absent in most cases of JIA except seropositive polyarticular JIA.
- **anterior uveitis**
  - **What eye condition is most commonly associated with this presentation? anterior uveitis.**
    - about 30–50% of children with JIA have uveitis at diagnosis, especially those who are antinuclear antibody (ANA) positive.
    - The uveitis is typically asymptomatic at onset and must be **screened** for with an ophthalmologic **slit lamp examination.**
    - Untreated uveitis can be associated with cataracts, glaucoma and macular oedema

- about 50–70% of people with severe uveitis develop visual impairment.
- **If a patient with (JIA) developed new-onset anterior uveitis despite treatment with subcutaneous methotrexate → adalimumab** (as adalimumab is more effective in treating uveitis than etanercept)

## Treatment

- Options for pharmacotherapy include NSAIDs, corticosteroids, methotrexate, and anti-TNF biologicals.
- Treatment with **IL-6 receptor antibody** has proved to be successful.
- As per NICE guidance, **if patient had not responded to methotrexate and should be considered for biologic therapy with either adalimumab, etanercept or tocilizumab.**

## Prognosis

- Anti-CCP antibodies indicate a poor prognosis.
- Early disease onset is associated with a greater degree of growth impairment and deformity.

# Seronegative spondyloarthropathies

## Seronegative spondyloarthropathies

**Common features:**

- Associated with HLA-B27
- **Rheumatoid factor negative - hence 'seronegative'**
- Peripheral arthritis, usually asymmetrical
- **Sacroiliitis**
- **Enthesopathy:** e.g. Achilles tendonitis, plantar fasciitis
- **Extra-articular manifestations:** uveitis, pulmonary fibrosis (upper zone).
- amyloidosis, aortic regurgitation.

## Classification

**axial:**

- radiographic axial spondyloarthritis (ankylosing spondylitis)
- non-radiographic axial spondyloarthritis

**peripheral:**

- psoriatic arthritis
- reactive arthritis
- enteropathic spondyloarthritis.

People with predominantly axial spondyloarthritis may have additional peripheral symptoms, and vice versa.

**Axial presentations of spondyloarthritis are often misdiagnosed as mechanical low back pain, leading to delays in access to effective treatments. Peripheral presentations are often seen as unrelated joint or tendon problems, and can be misdiagnosed because problems can move around between joints.**

# Ankylosing spondylitis (AS)

**Ankylosing spondylitis (AS) please refer to NICE guidelines 2017**

- Ankylosing spondylitis is **HLA-B27** associated spondyloarthropathy.
- It typically presents in **males** (sex ratio **5:1**) aged **20-30 years old.**
- It has **polygenic inheritance.**

## Features

- typically a young man who presents with lower back pain and stiffness of insidious onset
- stiffness is usually worse in the morning and improves with exercise
- the patient may experience pain at night which improves on getting up

**Referral for suspected axial spondyloarthritis:**

**If a person has low back pain that started before the age of 45 years and has lasted for longer than 3 months, refer the person to a rheumatologist for a spondylarthritis assessment if 4 or more of the following additional criteria are also present:**

- low back pain that started before the age of 35 years (this further increases the likelihood that back pain is due to spondylarthritis compared with low back pain that started between 35 and 44 years)
- waking during the second half of the night because of symptoms.
- buttock pain.
- improvement with movement.
- improvement within 48 hours of taking non-steroidal anti-inflammatory drugs

**(NSAIDs)**

- a first-degree relative with spondyloarthritis
- current or past arthritis
- current or past enthesitis
- current or past psoriasis.

If exactly 3 of the additional criteria are present, perform an HLA-B27 test. If the test is positive, refer the person to a rheumatologist for a spondyloarthritis assessment.

The commonest subtype HLA associations are **HLA B*2705** (Caucasians), **B*2704** (Chinese, Japanese) and **B*2702** (Mediterranean).
The B*2706 subtype is weakly associated and commonly found in normal South East Asian individuals.

## Clinical examination:

- **Reduced lateral flexion**
- **Reduced forward flexion** - **Schober's test** - a line is drawn 10 cm above and 5 cm below the back dimples (dimples of Venus). The distance between the two lines should increase by more than 5 cm when the patient bends as far forward as possible
- **Reduced chest expansion**
- **Sacroiliac joint tenderness**
- **Later (In the advanced stages of AS):** loss of lumbar lordosis, buttock atrophy and an accentuated thoracic kyphosis.

### Other features - the 'A's:

- **Apical fibrosis**
- **Anterior uveitis**
- **Aortic regurgitation**
- **Achilles tendonitis**
- **AV node block**
- **Amyloidosis**
- And cauda equina syndrome
- **Peripheral** arthritis (**25%**, more common if **female**)

## Investigation:

- Inflammatory markers (ESR, CRP) are typically raised although normal levels do not exclude ankylosing spondylitis.
- HLA-B27:
  - It is **not essential for the diagnosis** of AS.
  - **It not used as a screening test** for AS.
  - It is **of little use in making the diagnosis** and as it is positive in:
    - **90%** of patients with ankylosing spondylitis
    - 75% of patient with Reiter's syndrome.
    - 10% of normal patients
  - Its sensitivity and specificity depend on the **racial and ethnic background** of the patient.
  - Acute anterior uveitis is more common in B27 positive than negative patients.
- **Plain x-ray of the sacroiliac joints** is the most useful investigation in establishing the **diagnosis** and **monitoring, but** changes may not be seen for many years after the onset of symptoms. Radiographs may be normal early in disease, later changes include:
  - Sacroilitis: **sub-chondral erosions, sclerosis**
  - **Squaring of lumbar vertebrae**

- 'Bamboo spine' (late & uncommon)
- Syndesmophytes: due to ossification of outer fibres of annulus fibrosus
- Chest x-ray: apical fibrosis

- Spirometry may show a **restrictive** defect due to a combination of pulmonary fibrosis, kyphosis and ankylosis of the costovertebral joints.

40-year-old male. There is the typical appearance of bamboo spine with a single central radiodense line related to ossification of supraspinous and interspinous ligaments which is called dagger sign. Ankylosing is detectable in both sacroiliac joints

Kidney, ureter, bladder (K UB) view showing bamboo spine and fusion of both sacroiliac joints.

A. Fusion of the vertebral bodies and posterior elements gives the spine the classic "bamboo" appearance seen in ankylosing spondylitis. B. Note the marked kyphosis and the syndesmophytes that are the thin vertical connections between the anterior aspects of the vertebral bodies. . Syndesmophytes are due to ossification of outer fibres of annulus fibrosus They are located in the outer layers of the annulus fibrosis

## Diagnostic criteria:

**ESSG (European spondyloarthropathy study group) and amor criteria are the most sensitive ones available to date.**

## Management Medscape 2021:

The **best initial** therapy for **AS** is **NSAIDs** and **physiotherapy**.

- **NSAIDs** are the first-line treatment.
- **Physiotherapy**
- Encourage regular exercise such as swimming
- If symptoms are not controlled additional analgesics (for example, **amitriptyline**).
- Sulfasalazine.
- Corticosteroid injections or oral corticosteroids can be used.
- The DMARDs which are used to treat RA (such as **sulphasalazine**) are **only** really useful if there is **peripheral** joint involvement as it doesn't improve spinal mobility.
- The 2010 EULAR guidelines suggest: **'Anti-TNF** therapy should be given to patients with persistently high disease activity despite

conventional treatments' (severe ankylosing spondylitis which has failed to respond to NSAIDs.)

- Research is ongoing to see whether anti-TNF therapies such as etanercept and adalimumab should be used earlier in the course of the disease.

## Psoriatic arthropathy

- Psoriatic arthropathy **correlates poorly with cutaneous psoriasis** and **sometimes precedes the development of skin lesions by ten years.**
- Around **10%** of patients with skin lesions develop an arthropathy with males and females being **equally** affected.
- The condition can present with or without the associated psoriatic skin lesions or only with **nail malformations** (**onycholysis, transverse riding** and **pitting** of fingernails).
- If no obvious skin lesions are visible, the clinician should look for psoriasis in **hidden sites** such as the scalp, intergluteal cleft and umbilicus.
- **Extra-articular features** of the condition include **flexor tendon synovitis** and **uveitis.**
- It is associated with an increased frequency of **HLB-B7** and **HLA-B27.**

**There are 5 classic presentations (Types) of psoriasis:** based on the pattern of joint involvement.

- **Rheumatoid-like polyarthritis:**
  (that's why you have to exclude psoriasis in every rheumatoid case)
  - **Symmetrical polyarthritis**: (30-40%, **most common type**):
  - It affects wrists, hands, feet and ankles.
  - **The distal interphalangeal joints (DIP) are more commonly affected than the metacarpophalangeal joints.**
- Asymmetrical **oligoarthritis**: typically affects hands and feet (20-30%)
- **DIP** joint disease (10%)
- **Spondylitic pattern**: Sacroilitis
- **Arthritis mutilans** (severe deformity fingers/hand, 'telescoping fingers')

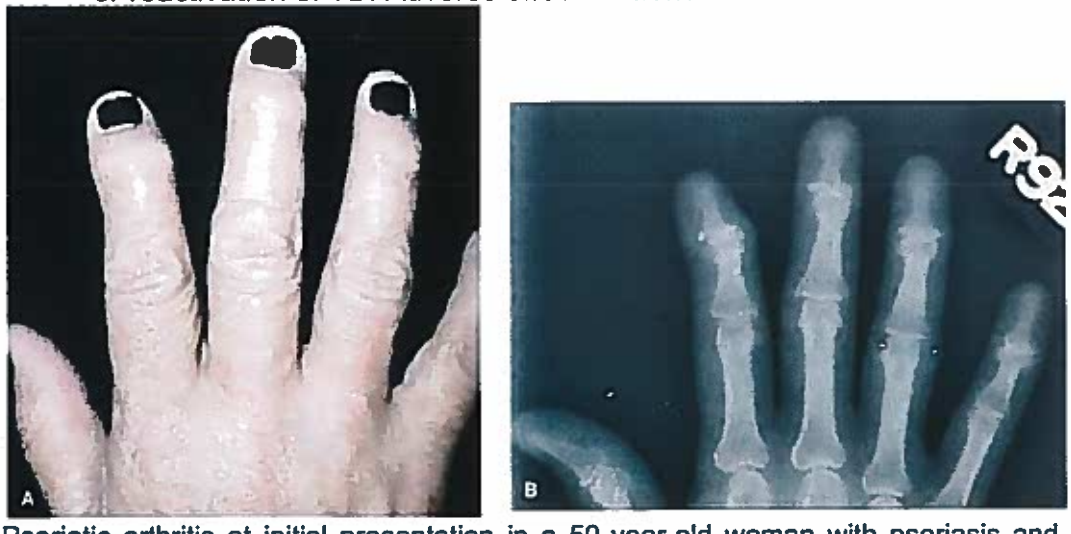
## Investigation

### X-ray

- often have the unusual combination of coexistence of erosive changes and new bone formation
- periostitis
- 'Pencil-in-cup' appearance

## Management:

- **Treat as rheumatoid arthritis, but better prognosis.**
- **DMARD** (e.g., methotrexate, leflunomide, sulfasalazine): to prevent joint damage from proliferative/ erosive changes in psoriatic arthritis.
- In the UK, **anti-TNF agents** are used for the treatment of psoriatic arthritis **only if** the patient fails to respond to an adequate **trial of two DMARDs.**
- ***Hydroxychloroquine* has been shown to exacerbate psoriatic skin** lesions in certain situations, and is therefore used with caution if at all.
- In patients with cutaneous psoriasis, ***systemic corticosteroids* predispose to pustular psoriasis,** and may result in a flare of skin psoriasis when they are stopped.
- **Ustekinumab:** It is a fully **human IgG1k monoclonal antibody to interleukin (IL)** 12/23. It is **not an anti-TNF agent** so no neutropenia or reactivation of TB. Adverse effect is: **dental infection.**




Psoriatic arthritis at initial presentation in a 50-year-old woman with psoriasis and new-onset hand pain. A. Note the prominent involvement of the distal interphalangeal joints. B. Radiography showing early psoriatic arthritis changes with periarticular erosions seen at the distal interphalangeal joints

Psoriatic arthritis of both knees. T his patient has asymmetric psoriatic arthritis in his hands.

Psoriatic arthritis with dactylitis and significant distal interphalangeal joint involvement. Note the destruction of the nails. almost all patients with psoriatic arthritis have nail involvement.

Psoriatic arthritis mutilans with severe destruction of the fingers.

# Reactive arthritis

**Reactive arthritis: is a sterile, inflammatory arthritis that is typically preceded by GIT or genitourinary infection occurring 1-4 weeks previously**

Reactive arthritis is one of the **HLA-B27 positive** associated seronegative spondyloarthropathies. It encompasses **Reiter's syndrome**, a term which described a classic **triad** of **urethritis**, **conjunctivitis** and **arthritis** following a **dysenteric** illness during the Second World War in 1916.

Later studies identified patients who developed symptoms following a sexually transmitted infection (**post-STI**, now sometimes referred to as sexually acquire reactive arthritis, **SARA**).

**Urethritis + arthritis + conjunctivitis** = reactive arthritis

Reactive arthritis >>>> **the Pt. can't see, can't pee, can't bend the knee**

## Epidemiology:

- Post-STI form much more common in men (e.g. 10:1)
- Post-dysenteric form equal sex incidence

The table below shows the organisms that are most commonly associated with reactive arthritis:

| Post-dysenteric form | Post-STI form |
|---|---|
| Shigella flexneri<br>Salmonella typhimurium<br>Salmonella enteritidis<br>Yersinia enterocolitica<br>Campylobacter | Chlamydia trachomatis |

## Features:

- **time course**
  - typically develops within 4 weeks of initial infection - symptoms generally last around 4-6 months
  - around 25% of patients have recurrent episodes whilst 10% of patients develop chronic disease

- **arthritis is typically** an asymmetrical oligoarthritis of lower limbs
- **dactylitis**
- **symptoms of urethritis**
- **eye**
  - conjunctivitis (seen in 50%)
  - anterior uveitis
- **Skin:**
  - **Circinate balanitis** (painless vesicles on the coronal margin of the prepuce),
  - **Keratoderma blenorrhagica** (palmo-plantar pustulosis) (waxy yellow/brown papules on palms and soles),
  - **Psoriasiform skin** and
  - **Nail and mucosal lesions**

Around **15-50 %** of patients with reactive arthritis have **recurrent** episodes whilst 15-30 % of patients develop chronic persistent arthritis or sacroiliitis.

**Differential diagnosis:**

**Gonococcal arthritis,acute septic arthritis,psoriatic arthritis,IBD arthritis and rheumatoid arthritis.**

**This disease is a clinical diagnosis**

## Management:

Bed rest and splinting.

Cold or warm compresses.

Passive then active exercise after resolving of acute inflammation.

**First line of treatment of reactive arthritis is oral NSAIDs** not antibiotics.

- Symptomatic: analgesia, **NSAIDS**, intra-articular steroids
- **Sulfasalazine** and methotrexate are sometimes used for persistent disease
- Symptoms rarely last more than 12 months.
- Antibiotics do not change the course of reactive arthritis, even when an infective cause is identified. However, some studies show that they may help to reduce the length of arthritis, particularly if Chlamydia is the triggering infection.
- If **Chlamydia** infection is suspected/confirmed >>> ttt by **Doxycycline.**
- **Refractory cases respond to sulfasalazine 2-3 gm/day.**

## Prognosis

- Prognosis with respect to long-term complications is better when **dysenteric** infection is the precipitant factor rather than **Chlamydial** infection.
- arthritis usually resolves in 3 months
- In general, symptoms last from a few weeks to around 6 months in total.
  - symptoms rarely last more than 12 months
- **Around 25% of patients have recurrent episodes**
- **10%** of patients develop **chronic disease**
- In **HLA-B27-positive** patients, **ankylosing spondylitis** may develop in up to **50%** of patients who have suffered an episode of **reactive arthritis**.
- HIV infection is associated with a higher risk of reactive arthritis
  - **HLA-B27** is found in 80–90 % of **Caucasians** with HIV-associated reactive arthritis,
  - while studies of **Africans** with HIV-associated reactive arthritis have found nearly all to be **HLA-B27-negative**
- Rarer **long-term complications** include:
  - urethral stricture,
  - cataracts, and aortic root necrosis.

Keratoderma blenorrhagica

**Gonococcal arthritis** is characterized by **dermatitis-polyarthritis-tenosynovitis** syndrome. It is the most common cause of septic arthritis in sexually active adults

# Systemic lupus erythematosus (SLE)

## Systemic lupus erythematosus (SLE)

SLE is a heterogeneous multisystem autoimmune inflammatory disease, in which ANA occur. Its presentation and course are highly variable, ranging from indolent to fulminant.

### Epidemiology:

- Much more common in **females (F:M = 9:1)**
- More common in **Afro-Caribbeans*** and **Asian** communities
- Onset is usually **20-40 years**
- Incidence has **risen** substantially during **the past 50 years** (**3 fold** using American College of Rheumatology criteria).

**The SLE criteria (ACR) are set for classification, statistical purpose and not diagnosis.**

For example; lady with ANA positive and malar rash may be developing lupus but yet not fulfilling the criteria. A lady with ANA positive and renal biopsy consistent with lupus is definitely has lupus in spite the fact that she is not fulfilling the criteria.

### Pathophysiology:

- Autoimmune disease
- Associated with **HLA B8, DR2, DR3**
- Thought to be caused by immune system dysregulation leading to immune complex formation
- Immune complex deposition can affect any organ including the skin, joints, kidneys and brain

*It is said the incidence in black Africans is much lower than in **black Americans** - the reasons for this are unclear

### Investigations

#### Immunology:

- **ANA** is highly sensitive and positive in over 95%, but not specific, **the** most reliable method is **the indirect immunofluorescence test. A titer as high as 1:160** Is needed to consider the test significantly positive, low titer of positive test of 1:40 is present in 10 % of normal population. **rim pattern** is the most specific pattern for SLE.

- **Anti-dsDNA: HIGHLY specific (100%),** but less sensitive (70%).
- **Anti-Smith: MOST specific (100%),** sensitivity (30%)
- also: **anti-U1 RNP**, **SS-A (anti-Ro)** and **SS-B (anti-La)**
- Low levels of **C3** and **C4** (C4a and C4b)
- 20% are rheumatoid factor positive.

SLE: ANA is 99% sensitive - anti-dsDNA & anti-Sm are 99% specific

**Anti-dsDNA antibodies** are **highly specific (100%)** for diagnosis of SLE.
Its level correlates with lupus **activity** especially with lupus nephritis.
However, they are **neither necessary, nor sufficient** in themselves for the diagnosis of SLE.
At any one time **only 50% patients with SLE have the anti-dsDNA antibody**, while only 70% patients with SLE develop anti-dsDNA antibodies at any one time during the course of their illness.

## Monitoring:

- **ESR:** during **active** disease the CRP is characteristically normal - a **raised CRP** may indicate underlying **infection.** (Very high CRP is unusual with SLE).
- Complement levels (C3, C4) are low during active disease (formation of complexes leads to consumption of complement) (↓C4 is early marker for disease activity) (although congenital C4 deficiency is itself a predisposing factor for SLE development so these tests must be interpreted with caution).
- **Anti-dsDNA titers** can be used for **disease activity monitoring** and often levels will rise just before a flare of disease. (But it is not present in all patients).

## Early markers of SLE disease activity:

- **High ESR.**
- **Low C4.**
- **High Anti-dsDNA titres.**
- **Falling Hb, TLC & PLT.**
- **Falling albumin.**
- Rising immunoglobulins (e.g. **high IgG**).

Although not mutually exclusive, different **ANA immunofluorescence patterns** suggest different diseases:

- **Anti-centromere** pattern: limited cutaneous systemic sclerosis
- **Cytoplasmic** pattern: Sjögren's syndrome, anti-synthetase syndrome
- **Nucleolar** pattern: diffuse cutaneous systemic sclerosis, polymyositis
- **Speckled** pattern: RA, **SLE**, Sjogren syndrome, systemic sclerosis, polymyositis, mixed connective tissue disease.

- **Homogenous (diffuse)** : SLE, mixed connective tissue disease

## Features:

### General features:

- Fatigue
- **Fever**
- Mouth ulcers
- Lymphadenopathy

### Skin:

- **Malar (butterfly) rash: spares nasolabial folds:**
  Can be flat but usually raised erythematous with papules and plaques,

Malar Rash

### These lesions heals without scarring.

- Discoid rash: scaly, erythematous, well demarcated rash in sun-exposed areas. Lesions may progress to become pigmented and hyperkeratotic before becoming atrophic.
- Acute cutaneous lupus erythematosus.
- Subacute cutaneous lupus erythematosus.
- Oral and nasal ulceration
- Raynaud's phenomenon
- Livedo reticularis
- Non-scarring alopecia(duo to the disease, scarring of discoid lupus or cyclophosphamide)
- **Hand rash: pathognomonic of lupus, erythematous lesions at the dorsum of the hand and fingers, affecting the skin between the joints (in contrast with Gottron papules of dermatomyositis that affect the MCP and PIP joints overlying skin)**

### Musculoskeletal:

- **Arthralgia**
- Non-erosive arthritis
- Jaccoud arthritis: MCP subluxation, ulnar deviation and swan neck deformity duo to lax joint capsule., tendons and ligaments. Later on will become fixed.
- Erosive symmetrical arthritis (Rhupus) with **negative** ANTI CCP ANTIBODIES AND **POSITIVE** Rh FACTOR.

Longstanding lupus erythematosus has caused swan-neck deformities without bone erosions. This is called Jaccoud arthropathy and is caused by synovitis and inflammatory capsular fibrosis

**Cardiovascular:**

- Myocarditis
- pericarditis: the most common cardiac manifestation

**Respiratory:**

- **Pleurisy & pleural effusions**: It is the **most common** manifestation of **SLE related lung disease** in up to **60%** of cases with reporting **pleuritic chest pain ± concomitant pleural effusion** >>> ttt: antibiotic (Amoxicillin).
- Chronic interstitial pneumonitis (CIP): in 15%.
- Fibrosing alveolitis

**Renal:**

- Proteinuria
- Glomerulonephritis (**diffuse proliferative class 4 IV glomerulonephritis** is the most common type)

**Neuropsychiatric lupus:**

- Anxiety and depression
- Psychosis
- Seizures
- **Amenorrhea**

The malar rash, arthralgia, lethargy and history of mental health >> points towards a diagnosis of SLE.
Remember that the CRP (in contrast to the ESR) is typically normal in SLE.

## Management

### Basics

- NSAIDs
- sun-block

### Hydroxychloroquine

- the treatment of choice for SLE

If internal organ involvement e.g., renal, neuro, eye then consider prednisolone, cyclophosphamide

## Complication

### Lupus patients are more prone to infection.

- Up to two-thirds of lupus patients will have some lung involvement during the course of their disease. The most common manifestations are pleuritis and pleural effusions.

**NB**: **Skin disease** may occur as part of SLE, or be present as cutaneous lupus erythematosus (frequently without any systemic disease), and with variable chance of progression to SLE.

- Discoid lupus erythematosus (**DLE**)
- Subacute cutaneous lupus erythematosus (**SACLE**)
- Acute cutaneous lupus erythematosus (**ACLE**)

In SACLE there is **ANA positive** in **60%** patients. However, only 10-15% progress to SLE with moderate disease activity. **80%** of patients are **anti-Ro antibody positive**.

## Discoid lupus erythematous

- Discoid lupus erythematous is a benign disorder generally seen more commonly in **younger African-Caribbean females**.
- It is a variant of SLE, in which skin involvement is the main feature.
- It **very rarely progresses to SLE** (in less than 5% of cases).
- Usually there is **negative ANA and anti-DNA.**
- It is characterised by follicular keratin plugs and is thought to be autoimmune in aetiology.
- Lesions are discrete **plaques**, often **erythematous**, covered by **scales** that **extend into dilated hair follicles**. These lesions most typically occur on the face, scalp, in the pinnae, behind the ears and on the neck. They can exist in areas not exposed to the sun.

- The lesions can progress, with active indurated erythema at the periphery.
- **Central atrophic scarring** is characteristic.
- Diagnosis is made by lesion biopsy.

## Features:

- Erythematous, raised rash, sometimes scaly
- May be **photosensitive**
- More common on face, neck, ears and **scalp**
- Lesions heal with **atrophy, scarring** (may cause **scarring alopecia**), and pigmentation

## Management:

- Topical steroid cream
- Oral antimalarials may be used second-line e.g. hydroxychloroquine
- Avoid sun exposure

Discoid lupus erythematous affecting the scalp

# Drug-induced lupus (DIL)

In drug-induced lupus not all the typical features of SLE are seen, with **renal** and **nervous** system involvement being **unusual.**

It usually **resolves on stopping the drug.**

Symptoms are said to appear some 3 weeks to 2 years after onset of therapy.

Patients with the HLA-DR3 antigen appear to be particularly at risk of developing drug-induced lupus.

Glomerulonephritis is unusual in drug-induced lupus

## Features:

- **Arthralgia**
- **Myalgia**
- **Malaise**
- **Skin** (e.g. **malar rash**) on face and upper chest in **25%** of sufferers.
- **Raynaud's** phenomenon is seen in around **25%.**
- **Pulmonary** involvement (e.g. pleurisy) are common
- **ANA** positive in 100%, but **dsDNA negative**
- **Anti-histone antibodies** are found in **95%**
- Anti-Ro, anti-Smith positive in around 5%
- **Hypergammaglobulinaemia (↑ IgG)**
- **Normal C3 and C4.**

A strongly positive ANA is a risk factor for developing drug-induced lupus, but a negative ANA would not exclude the diagnosis.

**Classically, drug-induced lupus erythematosus is characterised by**

- **Systemic disease** with **a lower incidence of nephritis**
- **Lack of cutaneous** involvement and
- The presence of **ant histone antibodies.**

**There are features which distinguish *drug-induced lupus* from idiopathic SLE:**

- **Males and females are equally affected** in drug-induced lupus, whereas idiopathic SLE affects females nine times more frequently.
- **Caucasians** are affected by drug-induced lupus more commonly than Afro-Caribbeans, whereas the inverse is true of idiopathic SLE.
- In addition, the **age** of onset is typically **older** in drug-induced lupus at **50-70** years, but this depends on the age at drug exposure.
- **Fever, arthralgia, serositis** and **ANA** occur at least as frequently in drug-induced lupus as idiopathic SLE.
- Haematological, renal and CNS involvement, and ds-DNA Ab are **rare.**

## Most common causes:

- Hydralazine
- Procainamide

## Less common causes:

- Phenytoin
- Valproate (Depakin)
- Carbamazepine
- Penicillamine
- Isoniazid
- **Sulfasalazine**
- **Minocycline** (ttt of acne)
- Chlorpromazine
- Methyldopa
- Beta blocker
- **ACEI (captopril)**
- **Statins**
- PTU
- Interferons
- Anti- TNF alpha agents (infliximab and etanercept).

## Treatment:

- **Stopping** of the offending drugs.
- Low dose corticosteroids can be used.

**EX: 16-year-old** girl presents with a **3 month history of polyarthralgia** and **marked early morning stiffness.**
Her symptoms respond well to diclofenac but she is becoming increasingly concerned about her symptoms which appear to be **progressing.** She is otherwise well apart from a history of **acne** which is well controlled on **minocycline.** Her mother has severe rheumatoid arthritis.
**Lab:** ESR= 50, CRP=100, RF=Negative, ANA=Strongly Positive, Anti-dsDNA=Negative, IgG=25↑ (N <15 g/L).
**The most likely cause is >>> Drug-induced SLE >>>**
**Treatment: Stop minocycline.**
**EX: A 22-year-old** woman is on sulfasalazine (2 gm/day) for three 3 for mild inflammatory arthritis. Over the last 2 wks. She has developed worsening arthralgia, swollen MCP joints, fatigue and low grade fever, oral ulcers, and widespread papular erythematous rash >>> **Drug-induced SLE,**
**Treatment Stop sulfasalazine.**

**MRCPUK part 2 exam:** A female diagnosed with epilepsy, suffering from an erythematous rash over sun-exposed areas of her skin. Antihistone antibodies are positive. **Which medication is the most likely cause of her rash?** >>> **Phenytoin, carbamazepine and lamotrigine** are associated with drug-induced lupus erythematosus

The **time** taken for symptoms to **resolve** after stopping minocycline is **highly variable, from a few days to 2 years.**
Typically, no further treatment is required but there are situations where corticosteroids or DMARDs are required to aid resolution.

A woman with drug-induced lupus

## Antiphospholipid syndrome

**Antiphospholipid syndrome (Hughes' syndrome) ALSO IN HEMATOLOGY**

It is an acquired disorder characterised by a predisposition to both **venous** and **arterial** thrombosis, **recurrent foetal loss** and **thrombocytopenia.**

It may occur as a primary disorder or secondary to other conditions, most commonly SLE.

It is **the most common cause** of **recurrent 1st trimester spontaneous miscarriage.**

It is thought to be the cause of complications in around 45/100,000 pregnancies.

Antiphospholipid antibodies (aPL) are present in **15% of women with recurrent miscarriage**, but in comparison, the prevalence of aPL in women with a low-risk obstetric history is less than 2%.

A key point for the exam is to appreciate that **Antiphospholipid syndrome causes a paradoxical rise in the APTT**. This is due to an ex-vivo reaction of the lupus **anticoagulant autoantibodies** with phospholipids involved in the coagulation cascade

**APLS >>> paradoxical ↑ APTT with ↓PLT**

APLS: **Prolonged PTT** in the presence of **normal PT**

## Features:

- **Recurrent foetal loss (3 unexplained mid-trimester miscarriage).**
- **Venous/arterial thrombosis**: DVT, PE, (**BRVO** Branch Retinal Vein Occlusion causing **sudden blindness**)
- **Thrombocytopenia**
- **Prolonged APTT**
- **Livedo reticularis**
- **Chorea**
- **Migraine.**
- **Liebman-sacks endocarditis**
- Other features: pre-eclampsia, pulmonary hypertension

It is associated with arterial and venous thrombosis and has a predilection for **the adrenal veins** causing **adrenal infarction** with consequent **hypoadrenalism**.

APLS may be a **primary** diagnosis or **may co-exist with SLE (secondary).**

## Associations other than SLE:

- Other autoimmune disorders: SLE, RA & Sjogren's.
- Lymphoproliferative disorders
- Phenothiazines (rare)

**Positive anticardiolipin antibodies** or a **lupus anticoagulant** are detected on 2 **separate** occasions, separated **by at least 6 weeks**.

### In pregnancy: the following complications may occur:

- Recurrent miscarriage.
- IUGR
- Pre-eclampsia
- Placental abruption
- Pre-term delivery
- Venous thromboembolism

## Management during pregnancy:

- **Low-dose aspirin** should be commenced once the pregnancy is confirmed on urine testing.
- **LMWH** once a foetal heart is seen on ultrasound. This is usually discontinued at 34 wks. gestation.
- Theses interventions ↑ **the live birth rate 7 folds.**
- Others: Omission of smoking and OCPs.

## Management - based on BCSH guidelines and EULAR:

- primary thromboprophylaxis
  - low-dose aspirin
- secondary thromboprophylaxis
  - initial venous thromboembolic events: lifelong warfarin with a target INR of 2-3

- recurrent venous thromboembolic events: lifelong warfarin; if occurred whilst taking warfarin then consider adding low-dose aspirin, increase target INR to 3-4
- arterial thrombosis should be treated with lifelong warfarin with target INR 2-3

## SLE and pregnancy

- **Unlike** many autoimmune diseases, systemic lupus erythematous (SLE) often becomes **worse** during **pregnancy** and the **puerperium.**
- Risk of maternal autoantibodies crossing placenta.
- Leads to condition termed **neonatal lupus erythematous**
- Neonatal lupus presents as erythematous macular rash on face or trunk, which may be photosensitive. It is a transient self-resolving illness due to passively transmitted maternal antibodies.
- Neonatal complications include **congenital complete heart block (CHB).**
- Strongly associated with **anti-Ro (SSA)** antibodies.
- **Risk of pre-eclampsia** is increased in SLE. It may be difficult to differentiate between pre-eclampsia and renal flare of SLE, and both may coexist. Differentiating features include raised anti-dsDNA antibody, decreased levels (C3 and C4) and response to steroids in the case of renal flare.

SLE >>> antibody associated with congenital heart block of baby is >>> **Anti-Ro**

**Complications of pregnancy in Sjogren's syndrome:**
**Anti-Ro**, and **anti-La** antibodies cross the placenta, and cause fetal AV nodal conduction defect, which may progress to complete heart block (**CHB**). This may be complicated by congestive cardiac failure (**CCF**), and **hydrops fetalis.**

**EX**: A 35-year-old woman who was 2 months postpartum presented with a 4 weeks history of **joint pain, facial rash** and **fever. ESR of 40** mm/hour (0-20).
The most likely diagnosis is >>> **SLE.**
The triad of fever, arthralgia and rash in a woman of childbearing age should suggest the diagnosis of SLE.

**Diffuse Infiltrative lymphocytic syndrome (DILS)** can present like **Sjogren's** syndrome with **parotid gland enlargement** and **sicca** symptoms (dry eye & mouth).
Extra glandular manifestations are common and it is rare for the patient to have positive autoantibodies unlike Sjogren's syndrome (i.e. **NEGATIVE** RF and ANA).
The weakness is due to a peripheral motor neuropathy.
Aseptic meningitis and cranial nerve palsies can also occur.
Lymphocytic interstitial pneumonitis is the most serious complication of DILS

# Crystal deposit

## Gout

- **Gout is the most common cause of inflammatory arthritis in men over 40 years of age.**
- **Gout** should not occur in premenopausal woman.
- Hyperuricemia and gout are strongly associated with obesity and the metabolic syndrome.
- The rheumatologist should look for gout in all undiagnosed joint conditions even if the serum uric acid level is normal, the involved joints are atypical, and the flare is chronic and polyarticular
- **Gout is a form of microcrystal synovitis caused by the deposition of monosodium urate monohydrate in the synovium. It is caused by chronic hyperuricaemia (uric acid > 0.45 mmol/l)**

### Resulting in one or more of the following:

1. Gouty arthritis.
2. Tophi.
3. Gouty nephropathy.
4. Uric acid nephrolithiasis.

It is caused by chronic hyperuricaemia (uric acid >7.0 mg/dl in males and > 6.0 mg/dl in females).

50% of all attacks and 70% of first attacks affect the **first metatarsophalangeal joint.**

### Predisposing factors:

**1) Decreased excretion of uric acid: (90% of cases of primary gout)**

- Chronic kidney disease
- Lead toxicity
- Pre-eclampsia
- Drugs: diuretics, low dose aspirin, pyrazinamide.
- High **alcohol** (more than 20 units for men, more than 15 units for women).

**2) Increased production of uric acid:**

- Lesch-Nyhan syndrome:
- Myeloproliferative/lymphoproliferative disorder, rhabdomyolysis and tumor lysis syndrome.
- Cytotoxic drugs
- Severe psoriasis
- Increase protein intake.

### 3) Lesch-Nyhan syndrome:

- Hypoxanthine-guanine phosphor-ribosyl transferase (HGPRTase) deficiency
- X-linked recessive
- Features: gout, renal failure, neurological deficits, learning difficulties, self-mutilation
- Patients with Lesch-Nyhan syndrome often take allopurinol for life.

**Drugs cause hyperuricemia duo to decreased renal excretion of urate:**

**Mnemonic ( CANT LEAP)**

- Cytotoxic agents: cyclosporine, tacrolimus.
- Alcohol.
- Nicotinic acid.
- Thiazides.
- Lasix.
- Ethambutol.
- Low dose ASA.
- Pyrazinamide.

### Uricosuric drugs:

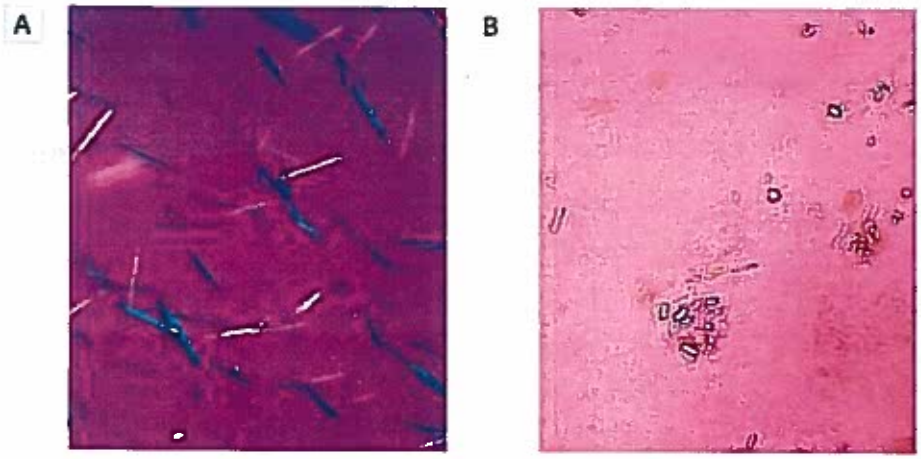
Losartan, amlodipine and fenofibrates, can cause mild reduction of uric acid level.

Patients with gout are often clustered with the **insulin resistance syndrome** known as metabolic syndrome: DM, HTN, hypertriglyceridemia, low HDL, although no evidence indicates that gout or hyperuricaemia cause any of these other disorders.

The relationship between serum uric acid and cardiovascular disease remains controversial.

- Low dose aspirin may exacerbate gout but **high dose aspirin is uricosuric**.
- Aspirin in a dose of 75-150mg is **not** thought to have a significant effect on plasma urate levels.
- The British Society for Rheumatology recommends **it should be continued if** required for **cardiovascular** prophylaxis.
- Many of the uricosuric drugs may be detrimental in renal failure and may not be effective.

Gouty joint aspiration >>> **Neutrophils** with **negative** birefringent crystals.




Compensated polarized light microscopy of synovial fluids (× 400). A Monosodium urate crystals show bright negative birefringence under polarized light and needle-shaped morphology. B Calcium pyrophosphate crystals show weak positive birefringence under polarized light and are few in number. They are more difficult to detect than urate crystals.

Most patients with hyperuricaemia never develop gout or stones. Treatment of these patients is not considered beneficial or cost-effective, and is therefore generally not recommended. The exception to this is in patients at risk of tumour lysis syndrome, where prophylactic treatment is recommended to reduce the incidence of renal impairment.

### Stages of gouty arthritis:

- asymptomatic hyperuricemia.
- acute gouty arthritis.
- Intercritical gout: the asymptomatic intervals between the attacks.
- chronic tophaceous gout.

Podagra. Typical inflammatory changes of gout at first metatarsophalangeal (MT P) joint

Tophaceous deposits on both elbows and one finger in a man with gout

An acute gouty arthritis attack of multiple finger joints in a 75-year-old man with gout. H is joints have been painful for 3 weeks. erythema from the acute inflammation is evident

Tophaceous deposits in the pinna of black man with gout.

Severe tophaceous gout with chronic gouty arthritis causing hand deformities and disabilities.

Severe tophaceous gout with large tophi and joint destruction of the hands.

Olecranon bursitis bilaterally in a man with gout.

## Management

### Acute management:

- **NSAIDs**
- **Intra-articular steroid injection**
- Colchicine: is an alternative but has a slower onset of action with main side effect is significant **diarrhoea and leukopenia.**
- **Corticosteroids.**
- **Rasburicase**: it is a recombinant urate oxidase which may be given during acute gout attack to allow allopurinol therapy to be commenced without the initial worsening of symptoms. It is also effective newer therapy in urate nephropathy in patients undergoing chemotherapy for haematological malignancy, it prevents and treat hyperuricaemia associated with tumour lysis syndrome (TLS).

**NB: Urate lowering agents should never be started until after complete resolution of the acute attacks and may be continued with NSAIDS OR colchicine for up to 6 months, nor should be stopped if an acute gouty attack occurs while the patient is taking them.**

If the patient is already taking XO inhibitors and happened to have an acute attack it **should be continued & add NSAIDS.**

### Indications for allopurinol and febuxostat (xanthine oxidase inhibitors):

- **Recurrent attacks** - the British Society for Rheumatology recommend 'In uncomplicated gout, uric acid lowering drug therapy should be started **if a second attack, or further attacks occur within 1 year'**
- Tophi.
- Renal disease.
- Uric acid renal stones.
- Prophylaxis if on cytotoxic or diuretics
- Patients with Lesch-Nyhan syndrome often take allopurinol for life.

**start allopurinol if >= 2 attacks in 12-month period**
**And should not be started until 2 weeks after an acute attack has settled**

### Side effects of allopurinol:

- 0.1-0.4 % allopurinol treated patients develop **allopurinol hypersensitivity syndrome (AHS).**
- This can present as a **severe multi-organ disease**, with non-blanching purpuric **rash**, **hepatic** and **renal** dysfunction, **eosinophilia**, and vasculitis, and has 20-25% mortality.

- 2% of patients on allopurinol develop itchy maculopapular rashes, and between 5-10% develop GIT dysfunction, and deranged liver function tests (LFTs).
- Risk factors for this include renal impairment, thiazide diuretic use, and recent initiation of allopurinol (weeks/months).
- AHS is caused by the direct toxic effects of oxypurinol, or by T cell activating effects of oxypurinol, allopurinol.
- Patients with AHS should not be rechallenged with the drug.
- Allopurinol **increases the anticoagulant effect of warfarin**
- 20% of patients on allopurinol, who are **prescribed amoxicillin or ampicillin**, develop a **rash**.

**Lifestyle modifications:**

- Reduce alcohol intake and avoid during an acute attack
- Lose weight if obese
- Avoid food high in purines e.g., Liver, kidneys, seafood, oily fish (mackerel, **sardines**) and yeast products

**Other points**

- consideration should be given to stopping precipitating drugs (such as thiazides)
- losartan has a specific uricosuric action and may be particularly suitable for the many patients who have coexistent hypertension
- increased vitamin C intake (either supplements or through normal diet) may also decrease serum uric acid levels

inhibits microtubule polymerization by binding to tubulin, interfering with mitosis. Also inhibits neutrophil motility and activity

**NB: Gout in pt. with DM and CKD:**

- **Colchicine** is useful in patients with renal impairment who develop gout **as NSAIDs are relatively contraindicated.** The BNF advises to **reduce** the dose by up to 50% if creatinine clearance is less than **50** ml/min and to **avoid** if creatinine clearance is **less than 30 ml/min.**
- Co-codamol 30/500 may be used as an adjunct but would not provide relief as monotherapy.
- Studies have shown that **paracetamol 1 g** combined with **codeine 60 mg** have the best analgesic outcomes **(the codeine dose is inadequate if < 60 mg).**
- **Prednisolone** is an option but would adversely affect his diabetic control can be used as prophylaxis at a dose of 10 mg/day or less.
- **Prednisolone** can be used instead of NSAIDS if it is contraindicated as in case of renal impairment or elderly with an increased risk of bleeding with warfarin.

- Corticosteroids are highly effective, and can be used where **NSAIDs are not tolerated**, or **in refractory disease** (**intra-articular**, oral, intramuscular, IV).
- If a patient with acute gout and cannot take NSAIDs as he has PUD, so **Intra-articular steroid injection** is the best alternative.
- If Pt. was on **warfarin,** whilst anticoagulation is not a contraindication to steroid joint **injection** it would make this option **less** attractive and **Colchicine** will be the drug of choice in this scenario.
- Colchicine had little or no interaction with warfarin but a case series was recently published that suggested INR may be increased in some patients prescribed colchicine, so **in patients on warfarin** with acute gout >>> 1st choice: **colchicine** and 2nd choice is **Rasburicase**
- **Hyperuricaemia** may be found in **asymptomatic** patients who have **not experienced** attacks of gout.
- Hyperuricaemia **may be associated with hyperlipidaemia** and **hypertension**. It may also be seen in conjunction with the **metabolic syndrome.**
- If diuretics are being used to treat hypertension an alternative antihypertensive should be considered, but they should not be stopped in the presence of CHF.
- If patient with an **acute gout flare up** and **mild renal impairment** >>>
  1) **Colchicine** and **increase the dose** to cope with the exacerbation up to a dose of 3 mg divided in 600 Mcg portions.
  2) A **short course of corticosteroids** (prednisolone 30 mg daily for 1 week) is a possibility **if** the patient fails to respond to the increased dose of colchicine.
  3) Adding NSAID may worse his kidney function.

## Pseudogout

Pseudogout is a form of microcrystal synovitis caused by the **deposition of calcium pyrophosphate (CPP) dihydrate in the synovium.**

### Risk factors:

- **Haemochromatosis (↑ transferrin saturation > 50 %)**
- **Wilson's** disease
- **Hyperparathyroidism** (ESRD).
- **Hypothyroidism**
- Acromegaly
- **Low magnesium, low phosphate**

## Features:

- **Red, hot, tender joint with effusion.**
- **Knee**, wrist and shoulders most commonly affected
- Joint aspiration: **non- or weakly-positively birefringent rhomboid or rod shaped crystals**
- X-ray: **chondro-calcinosis** (Non-specific changes such as **loss of joint space** and **linear calcification of the articular cartilage).**

**NB**: Pseudogout itself may cause (OA) osteoarthritic-like changes

## Management:

- Aspiration of joint fluid, **to exclude septic arthritis**
- **NSAIDs** or intra-articular, intra-muscular or oral **steroids** as for gout.
- **Colchicine** may be used if NSAIDs are contraindicated as in renal impairment.

**NB**: Elevated transferrin saturation may indicate haemochromatosis; a recognised cause of Pseudogout.A high ferritin level is also seen in haemochromatosis but can be raised in a variety of infective and inflammatory processes, including Pseudogout, as part of an acute phase response.

**EX**: A 72-year-old man presents with an **acutely painful right knee**.
On examination, he has a temperature of 37°C with a **hot**, **swollen** right knee.
Of relevance amongst his investigations, is a **TLC** of 12.6 ×109/L (4-11) and a knee radiograph which shows **reduced joint space** and **linear calcification of the articular cartilage.**
**Culture** of aspirated fluid reveals **no growth**.
The most likely diagnosis is >>> **Pseudogout**.
**DD:** Negative synovial fluid culture makes septic arthritis a less likely diagnosis.
**DD:** It is rare for rheumatoid arthritis to present as a large joint monoarthritis is a gentleman of this age.

# Inflammatory myositis

## Dermatomyositis

- Inflammatory disorder causing **symmetrical, proximal** muscle **weakness** and characteristic **skin** lesions.
- May be **idiopathic** or associated with **connective tissue disorders** or underlying **malignancy** (typically **lung** cancer, found in 20-25% - more if patient older, also **oesophageal carcinoma**).
- Polymyositis is a variant of the disease where skin manifestations are not prominent

### Skin features:

- Photosensitive.
- **Shawl sign: Macular rash over back and shoulder.**
- **Heliotrope rash** in the periorbital region and checks.
- **Gottron's papules** - roughened red papules over extensor surfaces of fingers at knuckles (pathognomonic).

If present between the knuckles it is pathognomonic of rheumatoid arthritis.

- **Telangiectasia** (Nail fold capillary dilatation).
- 'mechanic's hands': extremely dry and scaly hands with linear 'cracks' on the palmar and lateral aspects of the fingers

### Other features:

- **Proximal muscle weakness** +/- tenderness **with normal reflexes and sensation** and the **absence of fasciculations.**
- **Respiratory muscle weakness** with **decreased Vital capacity (VC)**
- Raynaud's
- **Interstitial lung disease**: e.g. Fibrosing alveolitis or organising pneumonia
- **Dysphagia,**
- Dysphonia
- The ocular muscles are very rarely involved unlike myasthenia gravis where this is a predominant feature.

### Investigations:

- ↑ **Creatine kinase** to 5-50 times the upper limit of normal.
- **EMG**
- **Skin and muscle biopsies are diagnostic for dermatomyositis.**

- ESR may be normal despite high disease activity.
- **ANA** positive in **60%**
- **Anti-Mi-2 antibodies** are highly **specific** for **dermatomyositis**, but are only seen in around 25% of patients.
- **Anti-Jo-1 antibodies** are not commonly seen in dermatomyositis - they are more common in **polymyositis** where they are seen in a pattern of disease associated with **interstitial lung disease** involvement, Raynaud's and fever.
- **Screen for malignancy**. (Abd-pelvis US, Mammography, CT chest, PSA, PR)

## TREATMENT:

- **Prednisolone** is the **mainstay** of Treatment, at an initial dose **1 mg/kg/day**. Most patients have a favourable response to corticosteroid therapy, and a 5-year survival rates approach 80%.
- When fail to show improvement, disease-modifying (**methotrexate**) or steroid-sparing agents (**azathioprine**) may be added.
- High protein diet and physiotherapy.

> ➢ Dermatomyositis antibodies >> **ANA most common, anti-Mi-2 Ab most** specific.
> ➢ **Anti-Jo-1 antibodies** are more common in **polymyositis** than dermatomyositis especially with coexistent ILD, Raynaud's phenomenon.

Polymyositis is the commonest cause of inflammatory muscle disease in people under 50-years-old (inclusion body myositis is the commonest in those over 50-years-old).

**EX:** Female patient 50 years old, **weakness**, pain and tenderness of shoulder girdle and thigh muscle, **discoloration around eyes, fingers telangiectasia, SOB, ↑ CPK 1000, ↑ESR, Anti-Jo-1 antibodies are positive** >>> **Polymyositis** with **ILD**.

**EX:** Old male 60 years with **intermittent** dysphagia to liquids and solids, purple **rash** on his face, **proximal muscle weakness** can't get up out of the chair, **+ve ANA** ... **Dermatomyositis** (NOT cancer oesophagus).

# Polymyositis

## Overview

- inflammatory disorder causing symmetrical, proximal muscle weakness
- thought to be a T-cell mediated cytotoxic process directed against muscle fibres
- may be idiopathic or associated with connective tissue disorders
- associated with malignancy
- dermatomyositis is a variant of the disease where skin manifestations are prominent, for example a purple (heliotrope) rash on the cheeks and eyelids
- typically affects middle-aged, female:male 3:1

## Features

- **proximal muscle weakness** +/- tenderness
- Raynaud's
- **mechanics hands** found in a subtype of polymyositis called anti-synthetase syndrome or Jo-1 syndrome. >>**fissuring and cracking on the distal digital pads of several fingers.**
- respiratory muscle weakness
- **interstitial lung disease**: e.g. fibrosing alveolitis or organising pneumonia
- **dysphagia**, dysphonia

## Investigations

- **elevated creatine kinase**
- other muscle enzymes (lactate dehydrogenase (LDH), aldolase, AST and ALT) are also elevated in 85-95% of patients
- EMG
- muscle biopsy
- **anti-synthetase antibodies**
  - anti-Jo-1 antibodies are seen in pattern of disease associated with lung involvement, Raynaud's and fever

## Treatment

- Prednisolone is the mainstay of treatment, at an initial dose of 1 mg/kg/d.
- In patients who fail to show improvement, disease-modifying steroid-sparing agents may be added.
- A high-protein diet and supervised exercise may further improve symptoms.

## Anti-synthetase syndrome

Anti-synthetase syndrome(sometimes considered as variety of dermatomyositis) associates with:

- **Raynaud's** phenomenon
- **Myositis**
- Fibrosing alveolitis, and
- Typical mechanic's hands (thickened, cracking, and peeling skin).
- **High CPK**
- **Positive Anti-Jo1 antibody**

## Inclusion body myositis (IBM)

IBM is an inflammatory condition that affects **the over 50s.**

Proximal muscles and finger flexors are predominantly involved, but distal muscle groups may also be involved.

The **onset** of muscle **weakness** in IBM is generally **gradual (over months or years)**

IBM occurs more frequently in **men** than women.

There is **no** association of IBM with malignancy.

Creatine kinase (CK) may be **normal.**

EMG shows a similar pattern in polymyositis and IBM - small short duration motor unit arrhythmias can complicate polymyositis and dermatomyositis, but not IBM.

**Muscle Biopsy with electron microscopy:** in IBM shows intranuclear or cytoplasmic tubofilaments on electron microscopy.

Polymyositis and dermatomyositis show a much better response to steroids than IBM.

| | Polymyositis | Dermatomyositis | IBM |
|---|---|---|---|
| Onset | Subacute | Subacute | **Slow** |
| age | Commonest < 50 years | Commonest < 50 years | **commonest > 50 years** |
| Affected muscles | Proximal | Proximal | **Proximal and distal** |
| symmetry | symmetrical | symmetrical | **Asymmetrical** |
| Common incidence | Female | Female | **Male** |
| Skin lesion | NO | **Characteristic rash** | NO |
| CK | Highly elevated (up to 50 fold) | Highly elevated (up to 50 fold) | **Mild elevated (up to 10 fold) or normal** |
| antibodies | anti-Jo-1 are more common | **anti-Mi-2 are highly specific** | anti-cN1A autoantibodies |
| Muscle biopsy | endomysial mononuclear **inflammatory infiltrate** and muscle fiber **necrosis.** | perivascular and interfascicular inflammatory infiltrates with adjoining groups of muscle fiber degeneration/regeneration | **intranuclear or cytoplasmic tubofilaments** |
| T cell | CD8 T cell | CD4 T cell | |
| Response to steroids | good | Good | **Poor** |

# Other rheumatic disease

## Mixed connective tissue disease

Mixed connective tissue disease (MCTD, Sharp's syndrome) is a rare, heterogeneous, multi-system autoimmune disorder.
It is a distinct clinical entity, but features of systemic lupus erythematosus (SLE), systemic sclerosis (SSc) and myositis may all be present.
It is associated with anti-U1 ribonucleoprotein (RNP) antibodies.
It is not to be confused with 'undifferentiated connective tissue disease.

### Epidemiology

- Male:female ratio 1:3
- Average age of presentation 30-40, may present in children
- Rare - incidence in adult population is estimated to be 2.1/million/year in one Norwegian study

### Presentation:

- Raynaud's phenomenon often precedes other symptoms and occurs in 90% of cases
- Polyarthralgia/arthritis
- Myalgia
- 'Sausage fingers'(dactylitis)

### Other clinically important features:

- Dermatological: photosensitive rash, scleroderma-like changes, alopecia
- Esophageal dysfunction
- Respiratory: pleuritis, pulmonary hypertension, interstitial lung disease
- Hematological: anemia, lymphadenopathy, splenomegaly, rarely TTP
- Cardiac: pericarditis, pericardial effusion, accelerated coronary artery disease
- Renal: glomerulonephritis (tends to be milder than SLE)
- Neuropsychiatric: seizures, mood disturbance

### Investigations:

- Exclude other connective tissue disease/vasculitis
- Bloods FBC: anemia, leucopenia, thrombocytopenia, U+E: renal impairment, CRP/ESR raised
- ANA (usually) positive, anti-Ds-DNA and scleroderma-specific antibodies (e.g. Anti-Scl70) are negative
- Anti-U1 RNP (an extractable nuclear antigen, ENA), must be positive*.
- Organ-specific investigations, e.g. ECG, echo, CT chest, MRI brain

## Management:

- No large-scale trials - patients have been included in trials for SLE/SSc and show similar levels of response to immunosuppression/DMARDs
- Calcium channel blockers may be used for the treatment of Raynaud's
- Proton pump inhibitors for reflux disease
- Endothelin receptor antagonists/prostacyclin analogues in pulmonary hypertension
- Smoking cessation, moderate exercise

## Prognosis:

- 1/3 long-term remission, 1/3 have chronic symptoms, 1/3 develop severe systemic involvement and premature death.

**Note** that anti-U1 RNP antibodies are not completely specific and may also be seen in definite SSc and SLE
Undifferentiated connective tissue disease refers to syndromes in which features of one or more 'classical' connective tissue disease may be present, but do not meet diagnostic criteria. Anti-U1 RNP is absent.

**Anti-ribonuclear protein (anti-RNP) = mixed connective tissue disease**

# Systemic sclerosis (SSc)

It is a **chronic autoimmune** disease condition of **unknown** aetiology characterised by increased **fibroblast** activity and **fibrosis** in a number of different organ systems in the form of hardened, sclerotic skin and other connective tissues.

It is 4 times more common in **females**.

## There are three patterns of disease:

### 1) Limited cutaneous systemic sclerosis:

- **Raynaud's** may be first sign
- Scleroderma affects **face** and **distal limbs** predominately
- Associated with **anti-centromere antibodies**
- CREST syndrome is an older term for the limited cutaneous form.
- **CREST syndrome** is a subtype of limited cutaneous systemic sclerosis: **C**alcinosis, **R**aynaud's phenomenon, **E**sophageal dysmotility, **S**clerodactyly, **T**elangiectasia
- Complications of CREST syndrome:
  - **Malabsorption** can develop in these patients secondary to **bacterial overgrowth** of the **sclerosed small intestine** (dysmotility secondary to infiltration of the intestinal wall with fibrous tissue).

- Also, unfortunately **pulmonary hypertension** is one of the more common late complications seen in such patient.

**NB: Lung involvement** is a frequent complication of systemic sclerosis, and can be split into **2 main syndromes**: a pulmonary vascular disorder evolving over time into relatively isolated **pulmonary hypertension** and **interstitial lung disease**.

**EX:** Female pt. with SOB, lung fibrosis, GERD, Raynaud's, +ve ANA >> Systemic sclerosis.

**The limited symptoms of scleroderma are referred to as CREST**

**C**alcinosis- calcium deposits in the skin

**R**aynaud's phenomenon- spasm of blood vessels in response to cold or stress

**E**sophageal dysfunction- acid reflux and decrease in motility of esophagus

**S**clerodactyly- thickening and tightening of the skin on the fingers and hands

**T**elangiectasias- dilation of capillaries causing red marks on surface of skin

**2) Diffuse cutaneous systemic sclerosis**

- Scleroderma affects **trunk** and **proximal limbs predominately**
- Associated with **scl-70 antibodies**
- Hypertension, **lung fibrosis** and renal involvement seen
  - Pulmonary involvement is the second commonest organ involvement after oesophageal disease and is **the leading cause of death.**
  - **Pulmonary fibrosis is associated with anti-Scl-70 antibodies in up to 70% of cases.**
  - scl-70 antibodies associated with a higher risk of severe interstitial lung disease

  - **Reduced DLCO is the earliest sign of pulmonary disease in systemic sclerosis, often before fibrotic changes manifest clinically.**
- Diffuse cutaneous systemic sclerosis may lead to **scleroderma renal crisis (SRC)** in up to 10% cases.
  - The underlying pathology of SRC is vasospasm,
  - Features
    - SRC may present with rapid onset renal failure,
    - malignant hypertension,
    - micro-angiopathic haemolytic anaemia with schistocytes.
    - Patients may develop symptoms of fluid overload.
  - Other risk factors for SRC include:
    - corticosteroid use (prednisolone more than 15 mg/day),
    - recent onset scleroderma (less than three years), and
    - involvement of other systems.
  - Treatment involves starting ACE inhibitors.
- Poor prognosis
- Whilst diffuse systemic sclerosis is associated with more severe and rapid internal organ involvement it is also seen in the limited form.

**3) Morphea (Localized Scleroderma)** (without internal organ involvement)

- Tightening and fibrosis of skin
- May be manifest as plaques (**morphoea**) or linear.
- This is a **well-defined oval to round plaque**. (Like a painless lesion to his left subcostal region, dry, indurated and slightly coarse to palpation).
- The pathogenesis is poorly defined.
- An autoimmune component is suggested by enhanced T helper 2 (Th2) dependent interleukin 4 (IL-4) activity, which in turn up regulates transforming growth factor beta (TGF -beta). TGF-beta stimulates fibroblast production of collagen and other extracellular matrix proteins.
- Lab:
  - Elevated **ESR** and **CRP**.
  - **Hypergammaglobulinaemia (↑IgM, IgG)**,
  - Peripheral **eosinophilia** and
  - **Anti-Cu/Zn superoxide dismutase Ab** have been found in up to **90%**.

## Treatment

- Superficial circumscribed morphea
  - Tacrolimus 0.1% **ointment** applied twice daily for 12 weeks may be a useful **first-line**
- Generalized, linear, or deep morphea
  - combination therapy with oral prednisone and methotrexate
  - To minimize the risk of relapse, the recommended treatment duration of MTX is at least 2 years.
  - Systemic corticosteroids can be helpful in the inflammatory phases of morphea, but they are not recommended for long-term monotherapy
  - Mycophenolate mofetil is a second-line

## Prognosis

- generally, resolves within 3–5 years, although sometimes a patch may persist for over 25 years.

A major complication is the development of **scleroderma renal crisis (SRC)**:

This is characterised by the **abrupt** onset of **severe hypertension**, usually with **retinopathy**, together with **rapid deterioration of renal function** and **heart failure**.

Renal crisis is linked with a positive ANA speckled pattern, anti-RNA polymerase I and II antibodies and absence of anti-centromere antibodies.

The clinical presentation is **typically** with the symptoms of **malignant hypertension**: Headaches, Hypertensive retinopathy associated with visual disturbances, Seizures, Heart failure and pulmonary oedema.

Renal biopsy is not necessary in patients presenting with classical features of renal crisis.

The hypertension is almost always severe with a **diastolic BP over 100 mmHg** in **90%** of patients.

There is **hypertensive retinopathy** in about **85%** of patients with exudates and haemorrhages and if severe, **papilledema.**

There may also be **microangiopathic haemolytic anaemia** (↓ Hb with blood film shows schistocytes and helmet cells), **thrombocytopenia** and raised renin levels. **Renal function is impaired and usually rapidly deteriorates.**

Scleroderma renal crisis is **a medical emergency**. Aggressive treatment is required to prevent the occurrence of irreversible vascular injury.

**First line** treatment is a gradual reduction in blood pressure (10-15 mmHg per day) with an **oral ACEIs** until the diastolic pressure reaches 85-90 mmHg.

**ACEI** will improve hypertension and slow further renal impairment.

**ACEI** is the treatment of choice in **systemic sclerosis** with **renal disease (↑ creat + HTN)**.

This approach leads to a **response in 90%** of patients by reversing the angiotensin-II mediated vasoconstriction.

An **abrupt fall** in BP should be **avoided** as it can further diminish renal perfusion and increase the risk of ATN. Therefore, ***parenteral antihypertensive*** agents (for example, IV nitroprusside or IV labetalol) should be ***avoided***.

**CCBs**, usually **nifedipine**, may be added where there is inadequate reduction of BP with ACEI alone.

Additional oral antihypertensive agents (for example, **labetalol**) can be used if required, and if pulmonary oedema is present a **nitrate infusion** may be indicated.

There is anecdotal evidence that IV prostacyclin helps the microvascular lesion without precipitating hypotension, and this is used in some UK centres.

## Antibodies:

- **ANA** positive in **90%**
- **RF** positive in 30%
- **Anti-centromere antibodies** associated with **limited** cutaneous S.S **(CREST).**
- **Anti-scl-70** antibodies associated with **diffuse** cutaneous S.S.(lungs)

Limited (**central**) **cutaneous** systemic sclerosis = anti-**centro**mere antibodies

Although ANA is positive in 90% of patients with systemic sclerosis, anti-centromere antibodies are the most specific test for limited cutaneous systemic sclerosis

## Management:

- Topical treatment for skin changes do not alter the disease course, but may improve pain and ulceration.
- NSAIDs.
- Steroids (limited benefit)
- CCB (Nifedipine)
- Bosentan (Dual Endothelin Receptor Antagonist)
- iloprost (Prostacyclin analogue)
- PDE-5 inhibitor.
- Methotrexate and cyclosporine.
- **Scleroderma renal crisis** >>>> **ACEI** (to control BP and delay progression to CRF)
- Active alveolitis >>>>> pulse cyclophosphamide + small dose steroids

## Scleroderma renal crisis

- A major complication of systemic sclerosis
- Severe and life threatening renal disease develops in approximately 10-15% of patients.
- Features
  - severe hypertension, with diastolic BP over 100 mmHg, usually with grade III or IV hypertension retinopathy, together with rapid deterioration of renal function and heart failure;
  - symptoms of malignant hypertension, with headaches, blurred vision, fits and heart failure.
  - haematological tests often demonstrate a thrombocytopenia and/or **microangiopathic** haemolysis.

### Treatment

- **Hypertension >> ACE inhibitor** (calcium channel blockers can be added).
  - **While ACE inhibitors are generally avoided in most patients with acute renal failure, scleroderma renal crisis is an exception to the rule** as long as renal function is closely monitored.
- Renal dialysis may be required.
- An excessive reduction in BP or hypovolemia (should be avoided) >>↓ renal perfusion >> acute tubular necrosis. Thus, **parenteral antihypertensive agents (such as intravenous nitroprusside or labetalol) should be avoided.**

# Relapsing polychondritis (RP)

Relapsing polychondritis is a multi-systemic condition characterised by repeated episodes of inflammation and deterioration of cartilage. This most commonly affects the ears, however, **can affect other parts of the body such as the nose and joints.**

## Key features:

- Ears: auricular chondritis, hearing loss, vertigo
- **Nasal: nasal chondritis → saddle-nose deformity**
- **Respiratory tract: e.g. hoarseness, aphonia, wheezing, inspiratory stridor**
- Ocular: episcleritis, scleritis, iritis, and keratoconjunctivitis sicca
- **Joints: arthralgia**
- Less commonly: cardiac valcular regurgitation, cranial nerve palsies, peripheral neuropathies, renal dysfunction

## Diagnosis:

- Various scoring systems based on clinical, pathological, and radiological criteria

## Treatment

- Induce remission: steroids
- Maintenance: azathioprine, methotrexate, cyclosporin, cyclophosphamide

# Still's disease in adults (= Adult-onset Still's disease (AOSD)

**Still's disease in adults (= Adult-onset Still's disease (AOSD)**

It is a **rare** systemic inflammatory disease.
It is typically affects **15–35-year-olds.**
Etiology is not clearly understood, but it is likely triggered by an infectious agent in a genetically predisposed host.
**Diagnosis is clinical**, and should include **exclusion** of infectious disease, neoplasms and other autoimmune disease.
Systemic features may precede the onset of arthritis.

## Features:

- **Polyarthralgia** (wrists, knees, ankles, elbows and metacarpophalangeal joints)
- **There is often an accompanying sore throat and myalgia.**
- Evanescent **salmon-colored** non-pruritic macular or macular-papular **rash: 90%** of patients and is often seen **only when the patient is febrile** and is easily missed.
- **Swinging pyrexia (intermittent fever)**: occurs once or twice daily and is described as quotidian returning to 37°C or below between episodes.
- **Serositis:** pleurisy with pleuritic chest pain, pericardial rub.
- **Reticuloendothelial activation: Lymphadenopathy & Hepatosplenomegaly**
  - ↑TLC, ↑ PLT
  - ↑ ESR, ↑ CRP, ↑ **Ferritin**
  - **RF, ANA**, and **anti-DNA: Negative** (Autoimmune Abs are negative).
  - **In between** the febrile episodes the patient feels rather **well**.

The diagnosis of Still's disease in adults can be challenging. The Yamaguchi criteria is the most widely used criteria and has a sensitivity of 93.5%.

## Diagnosis

- Diagnosis is clinical, and should include exclusion of infectious disease, neoplasms and other autoimmune disease.

## Management:

- **Half of the patients respond to NSAIDs.**
- Half of the patients respond to steroids even in full dose.
- Anti- IL-I(ANAKINRA OR CANACINUMAB) OR ANTI-IL6 (TOCILIZUMAB) can be reserved for refractory cases.

The prognosis is better than for adult RA.

## Macrophage activation syndrome:

Is a life-threatening complication of adult still disease, and manifest as fever, splenomegaly, cytopenia, hypertriglyceridemia, hypofibrinogenemia, marked elevation of s. ferretin, elevated soluble CD25, depressed natural killer cell activity and hemophagocytosis in bone marrow, spleen and lymph nodes.

**EX:** A **25**-year-old student presents to the casualty department with a **systemic illness**. She appears **unwell**, with a **swinging fever**, **3 kg weight loss** over 2 months, **generalised myalgia**, **polyarthralgia** affecting wrists, knees, ankles, elbows and metatarsophalangeal joints, and **a sore throat, pleurisy, pericardial rub, pericardial effusion, hepatomegaly, enlarged anterior cervical LN**.
**Investigations** demonstrate normochromic normocytic **anaemia 9.8 g/l**, TLC 20,000, PLT 500,000, **ESR 81** mm, **CRP 31 g/l**, serum **ferritin 1756 mg/dl**, **RF negative**, **ANA negative**, ASO titre <200iu.
The most likely diagnosis is >>>**AOSD**
**DD Polymyositis** is an inflammatory condition which typically presents with relatively painless, progressive, proximal muscle **weakness.**

**EX: Juvenile idiopathic arthritis (still's disease):**
Normally occurs in **younger** children, it may occasionally present in **adolescents** and young adults.
Up to 25% of cases have **+ve ANA**.
**Microcytic anaemia** which tends to be resistant to iron replacement.
**Pericarditis** is often found.
**Treatment**: NSAIDS, corticosteroids, methotrexate and anti-TNF biologicals.

## Familial Mediterranean Fever (FMF)

- Familial Mediterranean Fever (FMF, also known as **recurrent polyserositis).**
- It is an **autosomal recessive** disorder (**AR**) which typically presents by the second decade.
- It is more common in people of Mediterranean origin like **Middle East, Turkish**, Armenian, **Syria, Lebanon, Egypt, Israeli (Jewish)** and **Arabic** descent, but not exclusively.
- It relates to abnormal triggering of the inflammatory response and can lead to **AA type amyloid deposition** and therefore **renal failure**.
- However, patients with this condition frequently take high doses of analgesics and anti-inflammatory drugs which put them at risk from analgesic nephropathy.
- Patient is recurrently admitted to hospital and undergo extensive investigations and often abdominal surgery, but no specific pathology is found.
- Abdominal symptoms **often mimic an acute surgical abdomen** and consequently many patients have undergone unnecessary laparotomy.

- Despite the severity of the symptoms during an attack, patients quickly recover and are well between episodes.

## Features

**attacks typically last 1-3 days**

- Pyrexia (on-off).
- Abdominal pain with even tenderness and guarding (due to **Peritonitis**) (appendectomy scar is seen dt multiple admission with Abd pain).
- **Constipation** accompanying the fever is common and **diarrhoea** may follow its resolution.
- **Pleurisy**
- **Pericarditis**
- **Arthritis** in 75% of cases.
- **High ESR and CRP.**
- **Erysipeloid rash on lower limbs**
- **FMF>>>> Renal amyloidosis>>>> Nephrotic syndrome (proteinuria) >>>> might need renal transplantation**

## Diagnosis:

- **MEFV gene analysis for FMF**: it confirms the suspected diagnosis.
- **Renal biopsy**: it is **diagnostic** for amyloid associate nephropathy and analgesic nephropathy.
- **Rectal biopsy** followed by examination with polarised light leading to "apple-green" birefringence: to confirm amyloidosis.
- **Serum Amyloid P component (SAP scan)**: confirm the presence of amyloidosis.

The single most useful test to confirm the pathological basis of **amyloidosis** in **FMF** patient **when** develop **renal impairment** is >>> **Renal biopsy.**

## Management:

- **Colchicine** is extremely effective in **treating** and **preventing** attacks of FMF (↓ attack frequency).
- anakinra is indicated in those who do not respond to colchicine.
  - **Anakinra** is a drug used to treat rheumatoid arthritis. It is an interleukin 1 (IL1) receptor antagonist.

**NB:** Recurrent attacks of abdominal pain especially in young adults and may be misdiagnosed by surgeon >>> Think of **FMF** and **AIP** (Acute intermittent porphyria).
Whilst colchicine is of value in reducing amyloid deposition in FMF, there **is no evidence** that it has a **positive effect** in **amyloidosis** related to **other** underlying system inflammation like **rheumatoid arthritis**.

# Avascular necrosis (AVN)

- AVN may be defined as death of bone tissue secondary to loss of the blood supply. This leads to bone destruction and loss of joint function.
- It most commonly affects the **epiphysis of long bones such as the humerus & femur.**
- The main presentation is **pain** and **limitation of movements.**
- Both **night and rest pain** are present and **worsened with activity.**
- **Two forms** are existed: **traumatic** and **atraumatic.**
- Traumatic form occurs in nearly all fractures of the anatomic neck as well as in fractures or dislocations of the humeral or femoral head.

## Causes (risk factors for atraumatic form):

- **Long-term steroid use even low dose.**
- **Chemotherapy**
- **Alcohol** excess
- Haemoglobinopathies.
- Coagulopathies.
- Connective tissue disorders.
- trauma

## Features:

- Initially **asymptomatic**
- **Pain** in the affected joint

## Investigation:

- **Plain x-ray findings may be normal initially**
- **MRI is the investigation of choice.** It is **more sensitive than** radionuclide bone scanning

## Management

- joint replacement may be necessary

# Amyloidosis

**Secondary amyloid** A (AA) amyloidosis is an important complication of **rheumatoid arthritis (RA).**
It is caused by extracellular accumulation of AA fibrils, derived from the acute-phase-reactant **serum amyloid A protein**, within various tissues and organs. It is a significant cause of increased morbidity and early death in RA. Studies have shown that deposits of AA fibrils are not uncommon in RA (~20%).

**Any patient with longstanding RA who develops proteinuria, or intractable diarrhoea, should be investigated for AA amyloidosis >>> Rectal biopsy.**

## No blood test is diagnostic for amyloidosis.

Diagnosis therefore requires a **biopsy** and histological examination.
In order to start treatment as early as possible, a high-sensitivity site with a safe technique should be chosen. Subcutaneous fat, spleen, adrenal, liver, labia, salivary gland and gastrointestinal tract, **rectal** are frequent sites of AA amyloid deposition.

GI and rectal are recommended because their **sensitivities** are high and they can be performed as an **outpatient procedure**.

Non-invasive techniques, such as renal US, can be useful in assessing organ involvement, but cannot establish whether the findings are definitely related to amyloid.

The incidence correlates strongly with renal biopsy, but the procedure is associated with much lower risk.

Amyloidosis, as a **clinic-pathological descriptor** is used to denote the **in vivo**, **extracellular** deposition of material (**amyloid**) characterised by the following properties:

- **Haematoxylin and eosin** staining - **amorphous eosinophilic** appearance
- **Congo red** histological staining - **apple-green birefringence**
- **Electron micrography - fibrillar appearance**
- **X Ray diffraction** pattern - **beta pleated sheet structure**
- **Solubility in water** and buffers of low ionic strength.

## Treatment

- The only treatment is renal transplantation.
- It can be reduced by using high flux dialysis membranes in patients who are likely to be on dialysis for a prolonged period.

## Cardiac amyloidosis:

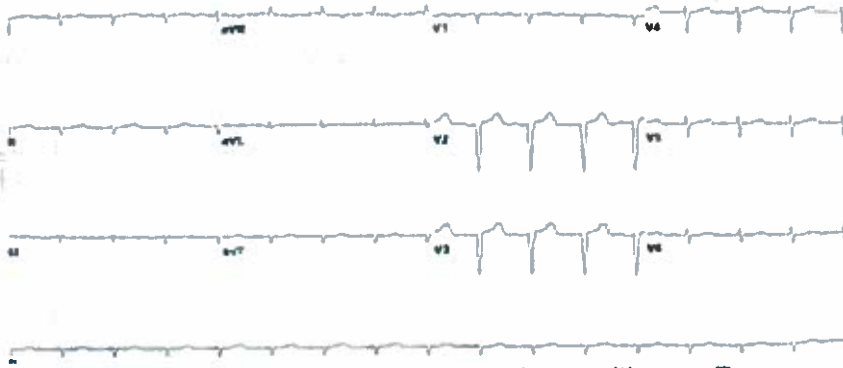
- Cardiac amyloidosis most commonly presents as restrictive cardiomyopathy, associated with AL Amyloidosis

**Presentation:** Typical presentation of right heart failure:

- Jugular venous distension
- Peripheral oedema
- Orthopnea and paroxysmal nocturnal dyspnea are typically absent

### Diagnosis

- Combination of low-voltage ECG and thickened ventricular walls is one of the characteristic features of cardiac amyloidosis.
- **Echocardiographic abnormalities** include:
  - dilatation of atria, thickened interatrial septum, diastolic dysfunction and small-volume ventricles.
  - The most distinctive feature of cardiac amyloidosis is a sparkling, granular appearance of myocardium, but this is a relatively insensitive feature occurring only in about 25% of cases.
  - Cardiac amyloidosis is associated with a 'global speckled' pattern on echo.



The ECG typically shows low-voltage complexes with poor R wave progression in the chest leads (a pseudoinfarction pattern).

### Management of AL

- The most effective treatment is autologous bone marrow transplants with stem cell rescues. However, many patients are too weak to tolerate this approach
- Other treatments can involve application of chemotherapy similar to that used in multiple myeloma. A combination of bortezomib and dexamethasone has been proposed, as has melphalan and dexamethasone.
- Digoxin is contraindicated in cardiac amyloidosis (restrictive cardiomyopathy)

# SAPHO syndrome

**SAPHO** is an acronym for **S**ynovitis, **A**cne, **P**ustulosis, **H**yperostosis, and **O**steitis.
It is characterised by **osteosclerotic bone lesions**, Bone biopsy can reveal sterile osteomyelitis, and a **variety of skin lesions**. The skin lesions are characterised by neutrophilic pseudo abscesses.

1) **Synovitis** - may be present rarely, and associates with erosions.
2) **Acne** - may be severe (conglobate or fulminans) and recur with new bony involvement.
3) **Pustulosis** - palmo-plantar pustulosis occurs in approximately **50%** of patients, other skin lesions may include psoriasis, **hidradenitis suppurativa**, acne, and rarely Sweet's syndrome.
4) **Hyperostosis** (increase in bone substance) and **osteitis** (inflammation of the bones) - the bony lesions typically involve the **acromioclavicular**, and **sternoclavicular** joints. Other sites include anterior chest wall, sternum, clavicle, pubic symphysis, spine, and mandible. These lesions are visualised on **99m technetium bone scan** or **MRI**.

The cause of the SAPHO syndrome is **unknown**.

## Diagnosis:

Should be suspected when there is an **association** of **rheumatic pain** with a **pustular skin disease.**

## Investigation

- skin lesions are characterised by neutrophilic pseudoabscesses.
- Bone biopsy can reveal sterile osteomyelitis.

## Treatment:

- SAPHO has **no** specific treatment, and some cases remit spontaneously.
- For the arthritic symptoms (i.e. NSAIDs and DMARDs).
- Isotretinoin and aciretin can be used to treat the skin disease.
- In the more severe cases corticosteroids, calcitonin, bisphosphonates and TNF-inhibitors can be used.

# Chronic fatigue syndrome (CFS)

Diagnosed **after at least 4 months** of disabling fatigue affecting mental and physical function more than **50% of the time** in the absence of other disease which may explain symptoms.

## Epidemiology:

- more common in **females.**
- past psychiatric history has not been shown to be a risk factor.

**Fatigue is the central feature; other recognised features include:**

- **Sleep** problems, such as insomnia, hypersomnia, unrefreshing sleep, a disturbed sleep-wake cycle
- Muscle and/or joint pains
- **Headaches**
- **Painful lymph nodes without enlargement**
- Sore throat
- **Cognitive dysfunction**, such as difficulty thinking, inability to concentrate, impairment of short-term memory, and difficulties with word-finding
- **Physical or mental exertion makes symptoms worse**
- General malaise or 'flu-like' symptoms
- **Dizziness**
- Nausea
- **Palpitations**

## Investigation:

- NICE guidelines suggest carrying out a large number of screening blood tests to exclude other pathology e.g. **FBC, U&E, LFT, glucose, TFT, ESR, CRP, calcium, CK, ferritin, coeliac** screening and also **urinalysis**

## Management:

- **Cognitive behaviour therapy** - very effective, number needed to treat = 2
- **Graded exercise therapy** - a formal supervised program, not advice to go to the gym
- 'Pacing' - organising activities to avoid tiring
- Low-dose amitriptyline may be useful for poor sleep
- Referral to a pain management clinic if pain is a predominant feature
- Better prognosis in children

children and young people only

# Fibromyalgia rheumatica (FM)

Fibromyalgia is a syndrome characterised by widespread pain throughout the body with **tender points at specific anatomical sites.**
The cause of fibromyalgia is **unknown** but may involve hyperexcitability within the spinal cord or brainstem, altered pain perception and somatisation.

## Epidemiology:

- It occurs in between 1-2% of the general population.
- **Women** are 10 times more likely to be affected
- Typically presents between 30-50 years old

## Features:

- Pain: at multiple site especially around the shoulders and neck, sometimes **'pain all over'**
- **Lethargy, Morning fatigue**
- Patients often **look unwell**, and may appear **depressed** and **anxious.**
- **Sleep disturbance**, headaches, dizziness are common
- **Diarrhoea** and **constipation** in 50% , often associated with abdominal bloating
- **Urinary frequency.**
- **Normal all investigations:** CBC, ESR, CRP, U&E, LFTs, Thyroid, and autoimmune screen.

**Diagnosis** is clinical and sometimes refers to the American College of Rheumatology
classification criteria which list 9 pairs of tender points on the body.
If a patient is **tender** in **at least 11 of these 18 points** it makes a diagnosis of fibromyalgia more likely.

## Management

- aerobic exercise: has the strongest evidence base
- **Explanation.**
- **Cognitive behavioural therapy.**
- **Analgesia.**
- **medication: pregabalin, duloxetine, amitriptyline**

**NB**: No role of Trigger point injections

**Key facts:**

**How to diagnose?**

- A female, presented with a feature of pain and **tenderness** over multiple area + **normal ESR** and CRP.

**What is the best management?**

- Treatment:aerobic exercise

# Osteoporosis

**Advancing age and female sex** are significant risk factors for osteoporosis. Prevalence of osteoporosis increases from 2% at 50 years to more than 25% at 80 years in women.

**In osteoporosis, there is decreased bone mass, but mineralization is normal.**

There are many other risk factors and secondary causes of osteoporosis. We'll start by looking at the most 'important' ones - these are risk factors that are used by major risk assessment tools such as FRAX:

- history of glucocorticoid use
- rheumatoid arthritis
- alcohol excess
- history of parental hip fracture
- low body mass index
- current smoking

## Other risk factors

- sedentary lifestyle
- premature menopause
- Caucasians and Asians
- endocrine disorders: hyperthyroidism, hypogonadism (e.g. Turner's, **testosterone deficiency),** growth hormone deficiency, hyperparathyroidism, diabetes mellitus
- multiple myeloma, lymphoma
- gastrointestinal disorders: inflammatory bowel disease, malabsorption (e.g. Coeliac's), gastrectomy, liver disease
- chronic kidney disease
- osteogenesis imperfecta, homocystinuria

**Medications that may worsen osteoporosis (other than glucocorticoids):**

- SSRIs
- antiepileptics
- proton pump inhibitors
- glitazones
- long term heparin therapy
- aromatase inhibitors e.g. anastrozole

## Investigations for secondary causes

If a patient is diagnosed with osteoporosis or has a fragility fracture further investigations may be warranted.

**NOGG recommend testing for the following reasons:**

- exclude diseases that mimic osteoporosis (e.g. osteomalacia, myeloma);
- identify the cause of osteoporosis and contributory factors;
- assess the risk of subsequent fractures;
- select the most appropriate form of treatment

**The following investigations are recommended by NOGG:**

- History and physical examination
- Blood cell count, sedimentation rate or C-reactive protein, serum calcium,

**albumin, creatinine, phosphate, alkaline phosphatase and liver transaminases**

- Thyroid function tests
- Bone densitometry ( DXA)

## Other procedures, if indicated

- Lateral radiographs of lumbar and thoracic spine/DXA-based vertebral imaging
- Protein immunoelectrophoresis and urinary Bence-Jones proteins
- 25OHD
- PTH
- Serum testosterone, SHBG, FSH, LH (in men),
- Serum prolactin
- 24 hour urinary cortisol/dexamethasone suppression test
- Endomysial and/or tissue transglutaminase antibodies (coeliac disease)
- Isotope bone scan
- Markers of bone turnover, when available
- Urinary calcium excretion

**So from the first list we should order the following bloods as a minimum for all patients:**

- full blood count
- urea and electrolytes
- liver function tests
- bone profile
- CRP
- thyroid function tests

## DEXA scan

### Basics:

- T score: based on bone mass of young reference population
- T score of -1.0 means bone mass of one SD below that of young reference population
- Z score is referred to the bone mineral density compared with that of a **'normal' age** matched subject adjusted for age, gender and ethnic factors

### T score:

- > -1.0 = normal
- -1.0 to -2.5 = osteopenia
- **< -2.5 = osteoporosis**

Osteoporosis in a man >>>>>> check testosterone

**Osteoporosis** is diagnosed according to the World Health Organisation **(WHO)** and International Osteoporosis Foundation **(IOF)** criteria which state:

- **Normal**: hip BMD greater than the lower limit of normal which is taken as 1 SD below the young adult reference mean **(T score ≥ -1).**
- **Osteopenia**: hip BMD between 1 and 2.5 DS below the young adult reference mean **(T score less than -1 but above -2.5).**
- **Osteoporosis**: hip BMD 2.5 SD or more below the young adult reference mean **(T score ≤ -2.5).**
- **Severe osteoporosis**: hip BMD 2.5 SD or more below the young adult reference mean in the presence of one or more fragility fractures **(T-score ≤ -2.5 PLUS fracture).**

## Osteoporosis: glucocorticoid-induced

Assessment for treatment - patients taking the equivalent of **prednisolone 7.5 mg or more each day for 3 months or longer**, and one of the following:

- Over the age of 65 years
- Have a history of a fragility fracture
- Have a **T-score less than - 1.5 SD**

The **T-score** of **less than -2.5** is indicative of osteoporosis. However **in patients on steroid therapy**, the T score of **less than -1.5 SD** is taken as a cut-off value to start osteoporosis therapy and an indication for a **bisphosphonate** and **Calcium** supplementation.

## Management of patients at risk of corticosteroid-induced osteoporosis

The RCP guidelines essentially divide patients into two groups.

- Patients over the age of 65 years or those who've previously had a fragility fracture should be offered bone protection.

- Patients under the age of 65 years should be offered a bone density scan, with further management dependent:

| T score | Management |
|---|---|
| Greater than 0 | Reassure |
| Between 0 and -1.5 | Repeat bone density scan in 1-3 years |
| Less than -1.5 | Offer bone protection |

The first-line treatment is alendronate. Patients should also be calcium and vitamin D replete.

## Osteoporosis: management

**RCP** guidance states that individuals should be given prophylaxis against osteoporosis if they:

- Are **under 65** years
- Require **steroids** for **longer than 3 months**, and
- Have a **T score** of **less than −1.5**

The initial treatment of choice is a **bisphosphonate**. Only if bisphosphonates are not tolerated, would alternatives be considered.

**NICE** guidelines were updated on the **secondary prevention** of **osteoporotic fractures** in **postmenopausal women.**

### Key points include:

- Treatment is indicated following **osteoporotic fragility fractures** in postmenopausal women who are confirmed to have osteoporosis (a **T-score** of **- 2.5 SD or below**).
- In **women aged ≥ 75 years**, a **DEXA scan may not be required** 'if the responsible clinician considers it to be clinically inappropriate or unfeasible'.

**EX: A 77-year-old woman** is discharged following a fractured neck of femur. On review she is making good progress but consideration is given to secondary prevention of further fractures. What is the most suitable management? >>> **Start oral bisphosphonate without waiting for a DEXA scan in such scenarios.**

- **Alendronate** is first-line
- Around 25% of patients cannot tolerate alendronate, usually due to upper gastrointestinal problems. These patients should be offered **Risedronate (Actonel ®)** or **Etidronate** (see treatment criteria below).
- Strontium ranelate and raloxifene are recommended if patients cannot tolerate bisphosphonates (see treatment criteria below).

- **Vitamin D and calcium** supplementation should be offered to all women unless the clinician is confident, they have adequate calcium intake and are vitamin D replete.
  - **If osteoporosis is established, the treatment includes 1500 mg/day of calcium and 400-800 pg /day of vitamin D**
  - Dietary intake of calcium should be:
    - 800-1000 mg/day in childhood through early adulthood
    - 1000-1200 mg/day in the middle years
    - 1500 mg/day in the elderly

## Treatment criteria for patients not taking alendronate

Unfortunately, a number of complicated treatment cut-off tables have been produced in the latest guidelines for patients who do not tolerate alendronate

These take into account a patients age, their T-score and the number of risk factors they have from the following list:

- parental history of hip fracture
- alcohol intake of 4 or more units per day
- rheumatoid arthritis

### The most important thing to remember is:

- the T-score criteria for risedronate or etidronate are less than the others implying that these are the second line drugs
- if alendronate, risedronate or etidronate cannot be taken then strontium ranelate or raloxifene may be given based on quite strict T-scores (e.g. a 60-year-old woman would need a T-score < -3.5)
- the strictest criteria are for denosumab.

## Detailed notes on treatment

### Bisphosphonates

- alendronate, risedronate and etidronate are all licensed for the prevention and treatment of post-menopausal and glucocorticoid-induced osteoporosis
- all three have been shown to reduce the risk of both vertebral and non-vertebral fractures although alendronate, risedronate may be superior to etidronate in preventing hip fractures
- ibandronate is a once-monthly oral bisphosphonate

### Vitamin D and calcium

- poor evidence bases to suggest reduced fracture rates in the general population at risk of osteoporotic fractures - may reduce rates in frail, housebound patients

**Raloxifene - selective estrogen receptor modulator (SERM)**

- has been shown to prevent bone loss and to reduce the risk of vertebral fractures, but has not yet been shown to reduce the risk of non-vertebral fractures
- has been shown to increase bone density in the spine and proximal femur
- may worsen menopausal symptoms
- increased risk of thromboembolic events
- may decrease risk of breast cancer

**Strontium ranelate**

- 'dual action bone agent' - increases deposition of new bone by osteoblasts (promotes differentiation of pre-osteoblast to osteoblast) and reduces the resorption of bone by inhibiting osteoclasts
- concerns regarding the safety profile of strontium have been raised recently. It should only be prescribed by a specialist in secondary care
- due to these concerns the European Medicines Agency in 2014 said it should only be used by people for whom there are no other treatments for osteoporosis
- **increased risk of cardiovascular events**: any history of cardiovascular disease or significant risk of cardiovascular disease is a contraindication
- **increased risk of thromboembolic events**: a Drug Safety Update in 2012 recommended it is not used in patients with a history of venous thromboembolism
- may cause serious skin reactions such as Stevens Johnson syndrome

**Denosumab**

- human monoclonal antibody that inhibits RANK ligand, which in turn **inhibits the maturation of osteoclasts**
- given as a single subcutaneous injection every 6 months
- initial trial data suggests that it is effective and well tolerated

**Teriparatide**

- recombinant form of parathyroid hormone
- very effective at increasing bone mineral density but role in the management of osteoporosis yet to be clearly defined
  - **Increased osteoblast activity** (the main effect)
  - **increased calcium absorption from the gut and**
  - **reduced calcium excretion from the kidney.**

**Indications**

- an alternative treatment option for the secondary prevention of osteoporotic fragility fractures in postmenopausal women who are:

- unable to take alendronate and risedronate, or strontium ranelate due to contraindication, intolerance or unsatisfactory response **and**
- age ≥ 65 years and have a T-score of ≤ –4.0 SD, **or** a T-score of ≤ –3.5 SD **plus** more than two fractures, **or**
- age 55–64 years and have a T-score of ≤ –4 SD **plus** more than two fractures.

**Disadvantage**

- Although this synthetic parathyroid hormone (PTH) analogue is an effective option for the treatment of severe osteoporosis, it is a **daily injectable**, and therefore, not considered by many patients, particularly those who don't likely injectables.

**Dose**

- The recommended dose is 20 micrograms administered once **daily** by subcutaneous injection in the thigh or abdomen.
- the maximum total duration of treatment was restricted, by the marketing authorisation, to 18 months.

**Contraindications include:**

- pre-existing hypercalcaemia,
- severe renal impairment,
- metabolic bone diseases other than primary osteoporosis (including hyperparathyroidism and Paget's disease of bone),
- unexplained elevations of alkaline phosphatase, and
- previous radiation treatment to the skeleton.

### Hormone replacement therapy

- has been shown to reduce the incidence of vertebral fracture and non-vertebral fractures
- due to concerns about increased rates of cardiovascular disease and breast cancer it is no longer recommended for primary or secondary prevention of osteoporosis unless the woman is suffering from vasomotor symptoms

### Hip protectors

- evidence to suggest significantly reduce hip fractures in nursing home patients
- compliance is a problem

## Falls risk assessment

- no evidence to suggest reduced fracture rates
- however, do reduce rate of falls and should be considered in management of high risk patients

MRI showing osteoporotic fractures of the 8th and 10th thoracic vertebrae.

## Osteomalacia

It results from inadequate mineralisation of the bone due to deficiency in Vit D.

**↓↓ Ca ↓↓ P ↓↓ vit D + ↑↑ ALP → osteomalacia**

### Basics:

- **Normal bony tissue** but **decreased mineral content**
- **Rickets** if when growing
- **Osteomalacia** if after epiphysis fusion

### Causes

- vitamin D deficiency
  - malabsorption
  - lack of sunlight
  - diet
- chronic kidney disease
- drug induced e.g. anticonvulsants
- inherited: hypophosphatemic rickets (previously called vitamin D-resistant rickets)
- liver disease: e.g. cirrhosis

## Features

- bone pain
- bone/muscle tenderness
- fractures: especially femoral neck
- proximal myopathy: may lead to a waddling gait

## Investigation:

- **bloods**
  - low vitamin D levels
  - low calcium, phosphate (in around 30%)
  - raised alkaline phosphatase (in 95-100% of patients)
- **X-ray:**
  - Children - cupped, ragged metaphysical surfaces;
  - Adults - translucent bands (**Looser's zones** or pseudo fractures):

**Osteomalacia X Ray >>> Looser's zones** it is **low density bands** extending **from the cortex inwards in the shafts of long bones.**

## Treatment: calcium with vitamin D tablets

The best source of vitamin D is **Cod liver oil** which provides around 1,300 IU per 15 ml serving.

The **low calcium** and **low phosphate** combined with the **raised alkaline phosphatase** >>> point towards **osteomalacia**.
**Hypophosphatemia** is **only** present in **25%** of cases of osteomalacia, and therefore normal level should not preclude the diagnosis.

**Ex: A 58-year-old woman C/O aches and pains in her bones. Generally weak and lethargic. low calcium, phosphate and vitamin D levels combined with a raised alkaline phosphatase and parathyroid hormone level. What is the most appropriate management?**
>> **Start vitamin D3 supplementation** (Δ >> osteomalacia)

# Osteopetrosis

## Overview

- Also known as **marble bone disease**
- Rare disorder of **defective osteoclast function** resulting in failure of normal bone resorption
- Results in dense, thick bones that are prone to fracture
- Bone pains and neuropathies are common.
- **Calcium, phosphate and ALP are normal**
- Stem cell transplant and interferon-gamma have been used for treatment

# Paget's disease of the bone

Paget's disease >>>> **old man, bone pain, raised ALP** (with **normal** Ca and PO4)

**EX: Old man** with **chronic back** and right **hip** pain **for several years** associated with **markedly elevated ALP** in the presence of **normal liver enzymes, normal calcium and normal ESR, difficulty hearing ± CHF >>> Paget's disease.**

- Paget's disease is a disease of increased but uncontrolled bone turnover.
- It is a **localised disorder of bone remodelling**.
- It is thought to be primarily a disorder of increased numbers of giant **osteoclasts**, with **excessive** osteoclastic resorption followed by increased osteoblastic activity in new bone formation and altered bone architecture.
- The structure of the new bone is disorganised and **mechanically weaker**, and therefore liable to **pathological fracture** and **deformity**.
- It can affect any bone, but is commonest in the **axial** skeleton, **long** bones and **skull**. The hands and feet are rarely affected.
- Both genetic and environmental factors are implicated, and it has been suggested paramyxovirus is involved.
- The **UK** has the **highest prevalence of Paget's disease** in the **world**.
- Paget's disease is common (UK prevalence **5%**) but **symptomatic in only 1 in 20 patients (5%).**

## Predisposing factors:

- Increasing age > 55 years
- Male sex
- Northern latitude
- Family history

## Clinical features - only 5% of patients are symptomatic:

- Bone pain (e.g. pelvis, lumbar spine, femur)
- Classical, untreated features: bowing of tibia, bossing of skull
- **Raised alkaline phosphatase (ALP) - calcium* and phosphate are typically normal.**
- Skull x-ray: thickened vault, osteoporosis circumscripta

- Femur x-ray: **Radiolucency of subarticular region** suggestive of **osteolysis and new bone formation**. Some areas of patchy
- **other markers of bone turnover include**
  - procollagen type I N-terminal propeptide (PINP)
  - serum C-telopeptide (CTx)
  - urinary N-telopeptide (NTx)
  - urinary hydroxyproline
- **bone scintigraphy**
  - increased uptake is seen focally at the sites of active bone lesions

**NB:** Calcium usually normal in this condition but hypercalcaemia may occur with prolonged immobilisation.

To confirm the diagnosis of Paget's disease >>> **Skeletal survey**.
**Indications for treatment include** bone pain, skull or long bone deformity, fracture, nerve compression, periarticular Paget's:

- **Bisphosphonate** (oral risedronate or **IV zoledronate**): is the drug of choice.
- Calcitonin is less commonly used now due to anaphylaxis.
- **Serial monitoring of alkaline phosphatase** can help to **monitor** treatment.

**Serum ALP every 6 months** as a non-invasive method, appears to be the best way to **monitor** Paget's disease **activity.**

In Paget's disease, if the patient is **asymptomatic, No** need for treatment and he should just be **monitored.**

## Complications:

- **Deafness or tinnitus** (VIII cranial nerve entrapment): in up to **50%** of cases.
- **Osteogenic sarcoma** (**1%** if affected for > 10 years) it carries a poor prognosis.
- **Fractures**
- **Skull thickening** and **spinal cord compression**
- **High-output cardiac failure**

The radiograph demonstrates marked thickening of the calvarium. There are also ill-defined sclerotic and lucent areas throughout. These features are consistent with Paget's disease.

Pelvic x-ray from an elderly man with Paget's disease. There is a smooth cortical expansion of the left hemipelvic bones with diffuse increased bone density and coarsening of trabeculae.

# Osteogenesis imperfecta (brittle bone disease)

Osteogenesis imperfecta (more commonly known as brittle bone disease) is a group of disorders of collagen metabolism resulting in bone fragility and fractures. The most common, and milder, form of osteogenesis imperfecta is type 1

## Overview

- **autosomal dominant**
- **abnormality in type 1 collagen** due to decreased synthesis of pro-alpha 1 or pro-alpha 2 collagen polypeptides

## Features

- presents in childhood
- fractures following minor trauma
- blue sclera
- deafness secondary to otosclerosis
- dental imperfections are common

## Investigations

- adjusted calcium, phosphate, parathyroid hormone and ALP results are usually normal in osteogenesis imperfect

# Bone tumors

## Benign tumors

| Tumour | Notes |
|---|---|
| **Osteoma** | • benign 'overgrowth' of bone, most typically occuring on the skull<br>• associated with Gardner's syndrome (a variant of familial adenomatous polyposis, FAP) |
| **Osteochondroma (exotosis)** | • most common benign bone tumour<br>• more in males, usually diagnosed in patients aged < 20 years<br>• cartilage-capped bony projection on the external surface of a bone |
| **Giant cell tumour** | • tumour of multinucleated giant cells within a fibrous stroma<br>• peak incidence: 20-40 years<br>• occurs most frequently in the epiphyses of long bones<br>• **X-ray shows a 'double bubble' or 'soap bubble'** appearance |

## Malignant tumors

| Tumour | Notes |
|---|---|
| **Osteosarcoma** | • most common primary malignant bone tumour<br>• seen mainly in children and adolescents<br>• occurs most frequently in the metaphyseal region of long bones prior to epiphyseal closure, with 40% occuring in the femur, 20% in the tibia, and 10% in the humerus<br>• x-ray shows Codman triangle (from periosteal elevation) and 'sunburst' pattern<br>• mutation of the Rb gene significantly increases risk of osteosarcoma (hence association with retinoblastoma)<br>• other predisposing factors include Paget's disease of the bone and radiotherapy |
| **Ewing's sarcoma** | • small round blue cell tumour<br>• seen mainly in children and adolescents<br>• occurs most frequently in the pelvis and long bones. Tends to cause severe pain<br>• associated with t(11;22) translocation which results in an EWS-FLI1 gene product<br>• x-ray shows 'onion skin' appearance |
| **Chondrosarcoma** | • malignant tumour of cartilage<br>• most commonly affects the axial skeleton<br>• more common in middle-age |

# Infection disorders

## Septic arthritis

### Pathophysiology

- most common organism overall is **Staphylococcus aureus**
  - in young adults who are sexually active, *Neisseria gonorrhoeae* is the most common organism (disseminated gonococcal infection)
- the most common cause is hematogenous spread
  - this may be from distant bacterial infections e.g. abscesses
- in adults, the most common location is the knee

### Features

- acute, swollen joint
  - restricted movement in 80% of patients
  - examination findings: warm to touch/fluctuant
- fever: present in the majority of patients

### Investigations

- **synovial fluid sampling** is obligatory
  - this should be done prior to the administration of antibiotics if necessary
  - may need to be done under radiographic guidance
- blood cultures: the most common cause of septic arthritis is hematogenous spread
- joint imaging

### Management

- intravenous antibiotics which cover Gram-positive cocci are indicated. The BNF currently recommends **flucloxacillin** or clindamycin if penicillin allergic
  - antibiotic treatment is normally be given for several weeks (BNF states 4-6 weeks)
  - patients are typically switched to oral antibiotics after 2 weeks
- needle aspiration should be used to decompress the joint
- arthroscopic lavage may be required
- if patient on warfarin, what is the most appropriate management of anticoagulation before joint aspiration and injection?
- If INR is within the therapeutic range >> no need to stop the warfarin or change the dose.

- The risk of a thrombotic episode if anticoagulation is changed outweighs any risk associated with injecting joint while taking anticoagulation.

**NB:** In gonococcal infection: standard aerobic and anaerobic cultures often **fail** to grow the organism; selective media are often required and the organism grows best in an atmosphere containing 3-10% $CO_2$.
**NB:** Disseminated gonococcal infection (DGI) with septic arthritis >>> ttt: **IV Ceftriaxone 1 g OD for 7 days.**

**NB:** Joint aspiration is mandatory in all patients with a **single** hot, swollen joint to rule out septic arthritis. If this was excluded in the above patient then intra-articular or system steroid therapy may be considered.

## Osteomyelitis

Osteomyelitis describes an infection of the bone. It may be subclassified into:

**haematogenous osteomyelitis**

- results from bacteraemia
- is usually monomicrobial
- most common form in children
- vertebral osteomyelitis is the most common form of haematogenous osteomyelitis in adults
- risk factors include: sickle cell anaemia, intravenous drug user, immunosuppression due to either medication or HIV, infective endocarditis

**non-haematogenous osteomyelitis:**

- results from the contiguous spread of infection from adjacent soft tissues to the bone or from direct injury/trauma to bone
- is often polymicrobial
- most common form in adults
- risk factors include: diabetic foot ulcers/pressure sores, diabetes mellitus, peripheral arterial disease

**Microbiology:** **Staph. aureus** is the most common cause except in patients with sickle-cell anaemia where *Salmonella* species predominate

**Investigations:** **MRI** is the imaging modality of choice, with a sensitivity of 90-100%

**Bone scintigraphy** (Gallium bone scan) if MRI is contraindicated (metal foreign body implants) → detects sites of infection

**X-ray shows:**

- still provide the best initial **screening** test for acute and chronic osteomyelitis.
- **Early stages (< 2 weeks of symptoms onset): typically no pathological findings**
- Later stages: bone destruction, **sequestrum** formation, periosteal reactions
- lytic lesion with sclerotic margins (**Brodie's abscess**)
  - a form of **chronic osteomyelitis**
  - thickened bone with irregular and patchy sclerosis that gives a honeycombed appearance.
  - Sequestra are seen as dense loose fragments lying within a cavity in the bone.
  - insidious onset (eg: 6-month history of gradually progressive swelling and pain)
  - often near the site of the metaphysis,
  - Deep 'boring' pain is often the predominant symptom.
- Osteomyelitis can cause a raised periosteum which is part of the radiographic sign known as the Codman triangle.

**Bone biopsy**

- **confirmatory test**
- Detects both osteonecrosis and the pathogen → confirms the diagnosis and helps guide more specific therapy

## Management

- flucloxacillin for 6 weeks
- clindamycin if penicillin-allergic
- Beta-lactams and vancomycin are commonly used as initial empiric therapy.
- Osteomyelitis from contiguous spread of infection
  - Piperacillin-tazobactam
  - Patients with penicillin allergy >> Clindamycin or metronidazole plus ciprofloxacin
  - If MRSA is suspected: >> Add vancomycin (or linezolid if allergic to vancomycin)

# Vasculitis

## Large vessels

### Temporal arteritis (TA) = (Giant cell arteritis) (GCA)

Temporal arteritis is **large vessel vasculitis** which **overlaps with polymyalgia rheumatica (PMR).**
GCA affects large and medium sized arteries, with a predilection for the external carotid, ciliary and retinal arteries.
Endovascular damage and cytokine-mediated inflammation causes local ischaemia.
Histology shows changes which characteristically **'skips'** certain sections of affected artery whilst damaging others.
Giant cell arteritis is a clinical emergency and should be treated without delay. It is not acceptable to give no treatment.
**20%** of patients develop **loss of vision**, which can be prevented with timely recognition and treatment. Visual loss typically occurs early in the course of disease and, once established, rarely improves.
As soon as the diagnosis is suspected, **high dose corticosteroids** should be given.

**Old man, Intermittent headache, lethargy with ↑ESR >>>> Temporal arteritis**

**Features:**

- typically patient > 60 years old
- usually rapid onset (e.g. < 1 month)
- headache (found in 85%)
- **jaw claudication (65%)**
- vision testing is a key investigation in all patients
  - anterior **ischemic optic neuropathy** accounts for the majority of ocular complications. It results from occlusion of the posterior ciliary artery (a branch of the ophthalmic artery) → ischaemia of the optic nerve head. Fundoscopy typically shows a swollen pale disc and blurred margins
  - may result in temporary visual loss - amaurosis fugax
  - permanent visual loss is the most feared complication of temporal arteritis and may develop suddenly
  - diplopia may also result from the involvement of any part of the oculomotor system (e.g. cranial nerves)

- tender, palpable temporal artery
- around 50% have features of PMR: aching, morning stiffness in proximal limb muscles (not weakness)
- also lethargy, depression, low-grade fever, anorexia, night sweats

In **elderly** people **GCA** is a **common presentation** of **acute monocular visual loss.**

## Investigations:

- **ESR > 50** mm/hr. (note that ESR < 30 in 10% of patients).
- CRP may also be elevated
- **Temporal artery biopsy (TAB)**: skip lesions may be present
- **CPK and EMG normal**

It is important to note that the **pathological findings** of giant cell arteritis (GCA) **persist for one to two weeks following initiation of corticosteroid**, and therefore treatment should not be delayed to obtain a biopsy.

## Treatment:

- Should be started **immediately** as soon as possible with **high-dose prednisolone (1mg/kg/day)** to reduce the chance of visual loss which is usually irreversible - there should be a **dramatic** and **diagnostic** response, if not the diagnosis should be reconsidered.
- Prednisolone therapy should not be delayed because involvement of the ophthalmic arteries can cause sudden unilateral irreversible visual loss.
- **Bone protection** and **proton-pump inhibitors** should be co-prescribed.
- Aspirin 75 mg OD is sometimes given as adjunct but higher doses are not recommended.
- Urgent ophthalmology review. Patients with visual symptoms should be seen the same-day by an ophthalmologist. Visual damage is often irreversible.

**As soon as the diagnosis is suspected, high dose corticosteroids should be given.**

**Current BSR guidelines recommend:**

- **Uncomplicated GCA** (no jaw or tongue claudication, or visual symptoms): **Prednisolone** 40-**60** mg daily.
- **Complicated GCA:**
  - Evolving visual loss or history of amaurosis fugax: **IV methylprednisolone 500 mg-1 g daily for 3 days, followed by oral corticosteroids.**
  - Established visual loss: at least 60 mg prednisolone daily.

Symptoms usually **resolve quickly**, often **within 2 or 3 days.**
In around **75% of cases** need steroid therapy **between 1-3 years.**
Once they and laboratory abnormalities resolve, the dose of corticosteroid can be **reduced** and usually **stopped within 2 years.**
The patient should be **monitored** for **recurrence** throughout the taper: ESR every 4 weeks for 2-3 months, then every 8-12 weeks until 12-18 m after cessation of therapy.

**NB:** If clinical scenario is like GCA PLUS prominent peripheral blood eosinophilia, high IgE, Sinusitis, Positive P-ANCA >>> should lead you to a diagnosis of **Churg-Strauss**.

## Polymyalgia rheumatica (PMR)

### Pathophysiology:

- **Overlaps with temporal arteritis (GCA)**
- The course of the disease is unpredictable, and 40% of patients also have giant cell arteritis.
- The cause is unknown, although studies showing a cyclical incidence have led to theories regarding an infectious trigger.
- Histology shows **vasculitis** with **giant cells**, characteristically **'skips'** certain sections of affected artery whilst damaging others
- Muscle bed arteries affected most in polymyalgia rheumatica.
- Diagnosis of PMR can prove difficult, and other inflammatory conditions should be excluded.
- Patients are **usually over 60 years**, and PMR is very rarely seen in the under 50s.

### Features:

- Typically, patient **> 60 years old**
- Usually **rapid onset (e.g., < 1 month)**
- **Pain** & **morning stiffness** in **proximal** limb muscles as **shoulder** and **pelvic** girdle muscles, classically symmetrical. (**Not weakness**).
- **Muscle weakness is NOT a feature of PMR**, but this can be difficult to assess in the presence of pain.
- **Muscle tenderness is NOT a specific feature of PMR**, and is not a classical finding. This is more suggestive of myositis or fibromyalgia.
- Also associated with a systemic inflammatory response and therefore constitutional symptoms as mild **polyarthralgia, lethargy**, depression, **low-grade fever, anorexia, loss of weight**, night sweats.

## Investigations:

- CBC: **Normochromic / normocytic anaemia.**
- ESR > 40 mm/hr (although this may be normal).
- **CPK and EMG normal**
- Reduced CD8+ T cells
- PMR is **not** usually associated with an **elevated** RF, but it is important to note that this RF is present in 1-2% of the normal population.

## Differential diagnosis

**Polymyositis** causes proximal muscle **weakness** in addition to pain, and **creatinine kinase** is typically raised.

**Polyarteritis nodosa (PAN)** is a small vessel vasculitis which does **not** commonly present with **isolated muscle** pain and stiffness. **Central** and **peripheral nervous** system signs are often present at diagnosis.

## Treatment:

- **Prednisolone** (maximum dose not exceed **20 mg/OD) >>** dramatic response within 2-4 days (patients should report **70% improvement** in symptoms within 3 to 4 weeks, and inflammatory markers should have normalised by this point).
- Relapse is common after cessation or reduction of prednisolone ttt.
- The median treatment time is **2 years**, but some people require substantially longer.
- Calcium and vitamin D supplementation should be initiated for all patients with PMR who are starting corticosteroid therapy.
- Bisphosphonates should be added for long term steroid therapy.
- In general, NSAIDs have little use and are associated with significant morbidity.
- There is little evidence for the use of **steroid-sparing agents**.
- **Methotrexate and azathioprine**
  - **If symptoms relapsed when the dose of prednisolone has been reduced below the current dose, >> Continue the current dose of prednisolone and start methotrexate**

**EX:** A 70-year-old man complains of **pain and stiffness in both his shoulders**. He has **lost one stone** in the last 8 weeks and complains of feeling **lethargic** with **loss of appetite.**
Labs: a **very high ESR (100 mm/hr), normochromic normocytic anaemia** and a **positive RF.**
The most likely diagnosis >>> **PMR.**

**NB:** In **polymyalgia rheumatica (PMR)/ GCA** >>> proximal muscle **stiffness** but **not weakness** in an elderly patient.
But, **Weakness and muscle pain** are the predominant features of **polymyositis/IBM.**

## Takayasu's disease (TD)

It is a **continuous** or **patchy granulomatous** inflammatory process involving macrophages, lymphocytes, and multinucleated giant cells which causes progressive **occlusive** disease of the **aorta** and **its branches.**

It is **very rare** in the **western** world with an annual incidence of between 2 and 3 per million.

Approximately 80% of patients are **women**, and the mean age of onset is **30** years.

### Clinical pictures:

- Presentation may be with **constitutional** symptoms such as fever, malaise, and weight loss;
- **Neurological** symptoms such as **TIA**; or vascular symptoms such as **claudication.**
- **Cardiac** features include **angina**, heart failure, and **aortic regurgitation.**
- **Renal**: mesangial proliferative GN.

**Treatment:** Corticosteroids ± steroid sparing drugs (azathioprine or methotrexate).

**With good care, 15-year survival rates approach 80%**

# Medium vessels

## Polyarteritis nodosa (PAN)

Polyarteritis nodosa (PAN) is a **systemic transmural necrotising vasculitis** that usually affects **medium** sized **arteries** with **necrotizing** inflammation leading to **aneurysm** formation, aneurysmal rupture, **thrombosis** and subsequently organ **ischaemia and infarction.**

It is a **multisystem** disorder, most commonly in **middle-aged men**.

**Angiography** demonstrates microaneurysms in affected organs, and biopsy shows necrotising inflammation. (Polymorph nuclear infiltrate and a homogenous eosinophilic (so called **fibrinoid necrosis**) appearance to the necrosed vessel walls). **NO** granulomatous inflammation.

Signs and symptoms are primarily attributable to diffuse vascular inflammation and ischaemia of the affected organs

It most commonly affects skin, joints, peripheral nerves, the GIT and the kidney. The **lungs** are usually spared.

Virtually any organ with the exception of the lung can be affected, with **peripheral neuropathy** and symptoms from **osteoarticular**, **renal** artery, and **cardiac**, **neurological** and **gastrointestinal tract** involvement being the most frequent clinical manifestations.

The most common causes of death are from **renal** (**HTN, renal failure**) and **cardiac** (coronary arteritis, **MI, pericarditis**) involvement.

A typical presentation is with **fever**, night sweats, **weight loss**, skin ulceration and tender nodules, and **severe muscle and joint pains (polymyalgia and polyarthralgia)**.

PAN is more common **in middle-aged men** and is associated with **hepatitis B infection.**

PAN can be further classified into systemic vs limited (cutaneous) and idiopathic vs hepatitis B, and this is important due to differences in pathogenesis and therefore treatment and prognosis.

## Features:

- **Fever**, malaise, poly-arthralgia, poly-myalgia.
- **Weight loss > 5 Kg.**
- **Hypertension** (**DBP > 90** mmHg).
- **Mononeuritis multiplex, sensorimotor polyneuropathy:** e.g. **foot drop.**
- **Testicular pain or tenderness (occasionally biopsy for diagnosis).**
- Abdominal pain (dt mesenteric ischemia).
- **Chest pain**
- Skin lesions: **purpura** and **Livedo reticularis.**
- **Renal** involvement: haematuria, nephritic, renal failure.
- Positive ANA
- pANCA are found in around **only 20%** of patients with **'classic'** PAN (i.e. is **not common**)
- Hepatitis **B** serology **(HBsAg)** positive in **30%** of patients (? Homosexuals or IV drugs abuser).

### ACR criteria for diagnosis of PAN (must have 3 of the following):

- Weight loss > 5 Kg.
- Skin lesions: **purpura** and **Livedo reticularis.**
- Testicular pain or tenderness.
- Myalgia, mono/polyneuropathy.
- **DBP > 90 mmHg.**
- **Renal impairment.**
- **HBV**

## Diagnosis:

By combination of **clinical** features plus **renal or mesenteric angiography** (microaneurysms).

**p-ANCA** is positive **only** in 20%.

- **ANCA is classically negative in PAN.**

### Biopsy

- should be performed **if angiography is not available or does not conclusively show a medium-vessel vasculitis.**
- Shows:
  - focal and segmental transmural necrotising inflammation with **fibrinoid necrosis** in medium-sized vessels.
  - **pleomorphic cellular infiltrate** of lymphocytes, neutrophils, macrophages, and eosinophils.
  - **granulomas are absent.**

## Treatment:

- For idiopathic PAN is currently **corticosteroids** and **cyclophosphamide**,
- For hepatitis B related disease Plasmapharesis and antivirals should be used.
- **Azathioprine** can be used as maintenance therapy, and typically has fewer side effects than cyclophosphamide.

**Cyclophosphamide >>> causes premature ovarian failure and infertility in both men and women.**

Livedo reticularis

Angiogram from a patient with polyarteritis nodosa. Both kidneys demonstrate beading and numerous microaneurysms affecting the intrarenal vessels. Similar changes are seen affecting the intrahepatic vessels with a few small microaneurysms noted. The proximal branches of the SMA appears normal; however, there are no normal straight arteries from the jejunal arteries and lack of normal anastomotic arcades and loops. This is associated with multiple microaneurysms.

## Thrombangitis obliterans (Buerger's disease)

- It is a disease of **small** & **medium sized arteries and veins** resulting in inflammation and ulceration.
- No excessive atheroma.
- Does **not** involve the **coronary** arteries like atherosclerosis.
- Occurs mainly in **cigarette smokers**, it has not been documented in non-smoker.
- Patients present with symptoms of **arterial ischemia (PVD).**
- **Migratory phlebitis in the superficial vein** is present in 40% of cases.
- The disease progress proximally, resulting in **gangrene of the digits (fingers and toes).**
- Negative RF, ANA, Anti-DNA.
- Diagnosis is usually clinical; however, arteriogram is also of benefit and will show occlusion of distal arteries of the hands and feet.

### Treatment

- is supportive and patients should **stop smoking.**

# Raynaud's phenomenon and disease

There is triad of colours: initial whitening of the fingers resulting from vasospasm, followed by blue discolouration and then reddening and pain.
Raynaud's phenomena may be:

- **Primary (Raynaud's disease)** or
- **Secondary (Raynaud's phenomenon)**

Raynaud's disease typically presents in young women **(e.g., 30 years old) with symmetrical attacks.**

Raynaud's **disease** (i.e **Primary**) presents in **young** women with **bilateral** symptopms

## Factors suggesting underlying connective tissue disease (i.e. secondary Raynaud's phenomenon):

- **Onset after 40 years**
- **Episodes lasting in excess of one hour**
  - episodes of secondary **Raynaud's** are longer
  - **Episodes of primary disease typically terminate within 15 minutes** following warming in, but can often be prolonged in secondary disease.
- **Unilateral** symptoms
- **Rashes**
- Presence of **autoantibodies**
- Features which may suggest RA or SLE, e.g. arthritis or **recurrent miscarriages.**
- **Digital ulcers, calcinosis, gangrene or severe ischaemia of one or more digits.**
- Very rarely: chilblains (pernio) are itchy, painful purple swellings which occur on the fingers and toes after exposure to the cold.

❶ Fingers become white due to lack of blood flow

❷ Fingers turn blue as vessels dilate to keep blood in tissues

❸ Fingers finally turn red as blood flow returns

**Note:** Raynaud's might be harder to detect in patients with darker skin. They might notice darkening of hands, arms, or face first.

## Primary Raynaud's(disease) can be diagnosed if all the following are present:

- No suspicion of underlying disease
- Symmetrical episodes affecting both hands, but not necessarily all fingers
- No tissue necrosis, ulceration, gangrene or severe ischaemia
- Normal nail-fold capillaries
- Normal ESR and negative anti-nuclear antibodies.

**NB:** Whilst it isn't a strict criterion given in the current guidance, it is recognised that episodes **typically terminate within 15 minutes** following **warming** in **primary** disease, but episodes tend to be **longer** in **secondary** Raynaud's and can be often in **excess of one hour.**

The most useful initial assessment to determine whether the Raynaud's is related to vasculitis or not >>> must include **nail fold capillary loop examination**, ideally by **capillaroscopy** or, if not available, by **ophthalmoscopy** using magnification >>> In CTD such as systemic sclerosis: dilated, distorted, missed nail fold capillary loops.

## Secondary causes (phenomenon):

- Connective tissue diseases (CTD): **scleroderma** (most common), RA, **SLE**, PAN, **Sjogren's** syndrome.

- **Type I cryoglobulinaemia**, cold agglutinins.
- **Leukaemia**
- **Polycythaemia.**
- **Thrombangitis obliterans (Burger's disease)**
- Use of vibrating tools
- Drugs: **oral contraceptive pill**, **ergot** (**NB**: Ergotamine **rather than pizotifen** is associated with Raynaud's phenomenon), βB, Vinblastine, Bleomycin.
- Cervical rib.

## Differential diagnosis of Raynaud's phenomenon includes:

- Chilblains (perniosis): erythematous itchy swellings on fingers and toes in response to cold.
- Acrocyanosis: continuous blueness of the extremities aggravated by cold.
- Erythromelalgia: painful erythema caused by paroxysmal dilatation of blood vessels.
- Vascular embolism.
- Livedo reticularis.
- Mottled, cyanotic discolouration of skin.

## Management:

- **Firstly, supportive** treatment: patients should **avoid** exposure to the cold and **stop** drugs- induced Raynaud's phenomenon.
- First-line treatment: vasodilation by **Dihydropyridine** CCBs e.g. **Nifedipine MR**
- In severe forms, IV prostaglandin, endothelin-1 receptor antagonists and phosphodiesterase-5 inhibitors are used.
- **IV prostacyclin** (epoprostenol) infusions: effects may last several weeks/months.
- Future treatment options may include selective alpha-2c adrenergic receptor blockers, tyrosine and Rho-kinase inhibitors and calcitonin gene-related peptide.
- ACEIs and anti-platelets have been trialled in small case series, although no definitive benefit has yet been shown.

**NB:** Around 2% of women and 6% of men with Raynaud's phenomenon develop systemic sclerosis.

# Small vessels

## ANCA associated vasculitis

Anti-neutrophil cytoplasmic antibodies (ANCA) are important as they are associated with a number of small-vessel vasculitides, including:

- granulomatosis with polyangiitis
- eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome)
- microscopic polyangiitis

**ANCA associated vasculitis is more common with increasing age. Whilst each condition has its own distinct features, there are a number of common findings:**

- **renal impairment**
  - caused by immune complex glomerulonephritis → raised creatinine, haematuria and proteinuria
- **respiratory symptoms**
  - dyspnoea
  - haemoptysiis
- **systemic symptoms**
  - fatigue
  - weight loss
  - fever
- **vasculitic rash**: present only in a minority of patients
- **ear, nose and throat** symptoms
  - sinusitis

### General approach to first-line investigations:

- **urinalysis for hematuria and proteinuria**
- **bloods:**
  - urea and creatinine for renal impairment
  - full blood count: normocytic anaemia and thrombocytosis may be seen
  - CRP: raised
  - ANCA testing (see below)
- **chest x-ray:** nodular, fibrotic or infiltrative lesions may be seen

### ANCA types

There are two main types of ANCA - cytoplasmic (cANCA) and perinuclear (pANCA). There is considerable overlap between which antibodies are found in which condition, but as a rule of thumb:

- cANCA - granulomatosis with polyangiitis

- pANCA - eosinophilic granulomatosis with polyangiitis + others (see below)

| | cANCA | pANCA |
|---|---|---|
| **Target** | Serine proteinase 3 (PR3) | **myeloperoxidase (MPO)** |
| **Granulomatosis with polyangiitis** | 90% | 25% |
| **Eosinophilic granulomatosis with polyangiitis** | Low | 50% |
| **Microscopic polyangiitis** | 40% | 75% |
| **Other associated conditions** | | Ulcerative colitis (70%)<br>Primary sclerosing cholangitis (70%)<br>Anti-GBM disease (25%)<br>Crohn's disease (20%) |
| **Use for monitoring** | Some correlation between cANCA levels and disease activity | Cannot use level of pANCA to monitor disease activity |

## General approach to management

Once suspected, ANCA associated vasculitis should be managed by specialist teams (e.g., renal, rheumatology, respiratory) to allow an exact diagnosis to be made. Kidney or lung biopsies may be taken to aid the diagnosis.

The mainstay of management is immunosuppressive therapy

# Henoch-Schonlein purpura

- Henoch-Schonlein purpura (HSP) is an **IgA mediated** small vessel vasculitis
- involving mainly the blood vessels of the skin, GI tract, the kidneys and the joints.
- 90% of cases of HSP occur in children aged 2-10 years but can occur in any age group.
- In children, (HSP) is the most common cause of vasculitis affecting the kidneys.
- typically commoner in males,
- may follow an infectious agent.

- It can present one to three days following infection of an IgA secreting mucous membrane (commonly following pharyngitis, but can occur following infection of the gastrointestinal tract, bladder or breast).
- An important risk factor in adults → chronic alcohol intake.
- associated with: *Helicobacter pylori*, hepatitis B and malignancy.

## Features

**HSP is characterised by the tetrad of:**

- purpura
- abdominal pain
- arthritis, and
- renal involvement (haematuria and proteinuria).

  - Patients with proteinuria have a worse prognosis than patients with haematuria alone.
- palpable purpuric rash (with localized oedema) over buttocks and extensor surfaces of arms and legs (due to a cutaneous vasculitis)
- abdominal pain (due to gut vasculitis, which may be severe in some cases, leading to bloody diarrhoea)
- polyarthritis (common symptom)
- features of IgA nephropathy may occur e.g. haematuria, renal failure
  - HSP nephritis becomes clinically manifest in only 20-30%.
  - It usually presents as macroscopic haematuria and proteinuria
  - Of those patients with renal involvement, as many as 10% may develop chronic renal failure and end-stage renal disease. However, fewer than 1% of all patients with HSP suffer this poor prognosis.

## Diagnosis:

- **Skin biopsy** and immunofluorescence demonstrate **leukocytoclastic vasculitis with IgA deposition**, (meaning lots of white blood cells in the skin around small blood vessels) **which is pathognomonic for HSP.**
  - Immunofluorescence studies will reveal >> **IgA deposits within blood vessel walls**

## Treatment

- analgesia for arthralgia
- treatment of nephropathy is generally supportive.
  - **All patients with hypertension and proteinuria (greater than 1 g/day) should be started on an angiotensin-converting enzyme (ACE) inhibitor**, which may control the BP and proteinuria.

- Once the BP has been controlled, patient should have a renal biopsy, and if this showed changes of a crescentic glomerulonephritis (GN), then an immunosuppression regime similar to that used in renal vasculitis should be started (probably with high dose steroids in the first instance +/- cyclophosphamide).
- There is inconsistent evidence for the use of steroids and immunosuppressants
- Management of HSP in adults often involves the use of immunomodulatory or immune-suppressive regiments (in contrast to children where the majority of cases resolve spontaneously).

## Prognosis

- usually excellent, HSP is a self-limiting condition, especially in children without renal involvement
- There is often a more complicated course in adults, and 50% of patients who present with renal involvement develop renal insufficiency.
- around 1/3rd of patients have a relapse

**Henoch-Schonlein purpura (HSP) is the tetrad of:**

1. **Purpura**
2. **Abdominal pain**
3. **Renal involvement (haematuria and proteinuria)**
4. **Arthritis**

**Incidence: most common in children <17 years.**

**Mechanism: IgA mediated small vessel vasculitis.**

**Diagnosis: Skin biopsy >> leukocytoclastic vasculitis with IgA deposits within blood vessel walls.**

**Treatment:**

- **For pain: 1st line >> naproxen. 2nd line >> prednisone.**
- **for hypertension and proteinuria >> ACE inhibitor.**

**Prognosis: self-limited >> Full renal recovery.**

**MRCPUK part 1 exam: What is the most likely renal outcome in Henoch-Schonlein purpura? Full renal recovery**

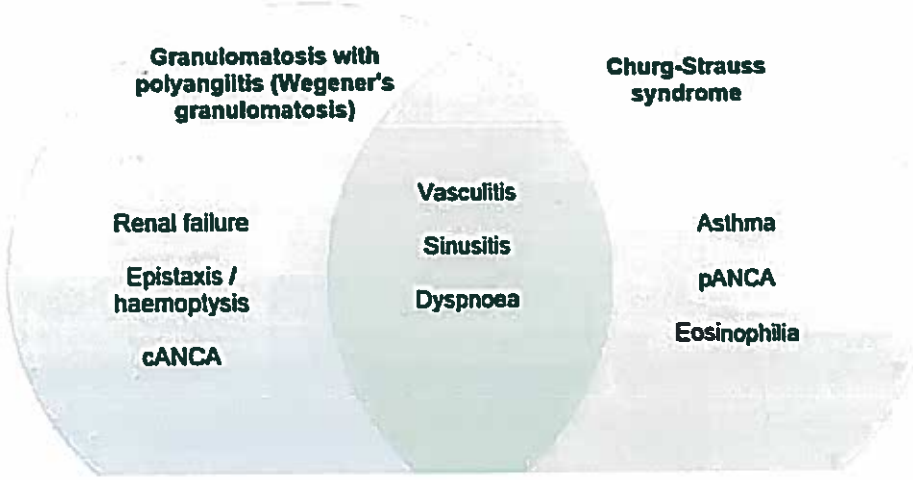
Síntomas y signos típicos de la púrpura de Henoch-Schönlein
Manchas rojizas y púrpuras con relieve o áreas con moretones, principalmente en las nalgas, las piernas y los pies. En algunas personas, las manchas pueden aparecer en el tronco, los brazos y las manos.
Dolor abdominal, nauseas, vómitos y diarrea sanguinolenta
Inflamación y dolor articulares
Edema (hinchazón) de pie y tobillo
C.Lynm

## Microscopic Polyangiitis

- **PR3 antibody is associated with Wegener's granulomatosis,**
- **MPO antibody is associated with microscopic polyangiitis**
  - Microscopic polyangiitis is similar to wegener's granulomatosis except in 3 things:
    1. it only affects small blood vessels in the lungs or kidneys.
       - No nasopharyngeal damage like wegener's
    2. Associated with p-ANCA antibodies.
       - anti-MPO (pANCA, 45%) antibody is strongly positive than anti-PR3 (cANCA, 30%)
    3. No granuloma on biopsy

| **Microscopic polyangiitis is similar to Granulomatosis with polyangiitis (Wegener's granulomatosis) except in 3 things:** |
|---|
| **1. it only affects small blood vessels in the lungs or kidneys. (No nasopharyngeal damage like wegener's)** |
| **2. Associated mor with anti-MPO (pANCA, 45%) than anti-PR3 (cANCA, 30%)** |
| **3. No granuloma on biopsy** PassOnExam |

# Granulomatosis with polyangiitis




## Overview

- Granulomatosis with polyangiitis is now the preferred term for Wegener's granulomatosis.
- It is an autoimmune condition associated with a necrotizing granulomatous vasculitis, affecting both the upper and lower respiratory tract as well as the kidneys.
- **the classical triad** consists of
  1. necrotising granulomatous inflammation of the respiratory tract,
  2. glomerulonephritis
  3. small-vessel vasculitis.

## Features

- upper respiratory tract: epistaxis, sinusitis, nasal crusting
- saddle-shape nose deformity
- lower respiratory tract: dyspnoea, haemoptysis
  - **migrating alveolar shadowing**
- rapidly progressive glomerulonephritis ('pauci-immune', 80% of patients)
  - It usually presents with rapidly progressing renal failure (within three months), proteinuria and microscopic haematuria.
- also:
  - vasculitis (causing carotid artery tenderness)
  - vasculitic rash,
  - eye involvement (e.g. proptosis),
  - cranial nerve lesions

## Investigations

- c-ANCA (PR3-ANCA (targeting peroxidise-3) positive in > 90%, p-ANCA (MPO-ANCA (targeting myeloperoxidase) positive in 25%
  - cANCA directed against proteinase-3
  - cANCA is highly specific, but is **found in only 50% of patients with disease localised to the respiratory tract** and 95% with generalised Wegener's.
    - In active Wegener's disease **with renal involvement** cANCA is **highly sensitive and specific.**
  - After disease remission cANCA **may remain elevated for years**, and is **not useful in evaluating patients for relapse.**
- chest x-ray: wide variety of presentations, including cavitating lesions
- tissue biopsy
  - renal biopsy:
    - epithelial crescents in Bowman's capsule
    - Kidneys show vasculitis and glomerulonephritis and **occasional** (NOT always ) granulomata
  - **Lung biopsy has a high diagnostic yield**
    - show vasculitis and granulomas
  - Biopsy of the upper respiratory tract shows granulomas **but not vasculitis.**

## Management

- steroids
  - **Prednisolone** is given in doses of around 1 mg/kg per day initially, after which the dose is reduced rapidly, typically at weekly intervals.
  - **In case of renal failure with indications for dialysis, the initial management >> Methylprednisolone**
    - **Methylprednisolone should be given immediately, followed by haemodialysis and then cyclophosphamide.**
- cyclophosphamide (90% response)
  - **The combination of prednisolone and cyclophosphamide is now established as the standard therapy and the treatment of choice for induction of remission in Wegener's granulomatosis**
  - **Cyclophosphamide**: Traditionally, oral dose (2 mg/kg per day), but latterly intravenous boluses have proved increasingly popular, given in doses of 0.5-0.75 g/m2 body surface area at intervals of 2 weeks (at least for short periods) to 2 months.
  - **If a patient had a vasculitic neuropathy. Current practice is to use cyclophosphamide for induction therapy.**

- Both rituximab and methotrexate have also been used for induction therapy in ANCA-associated vasculitis, although they would not be first-line treatment.
- Azathioprine is used as maintenance treatment following cyclophosphamide
- ciclosporin is rarely used in the management of ANCA-associated vasculitis.
- Evidence from controlled trials suggests that once remission is achieved azathioprine or methotrexate may be reasonable alternatives to cyclophosphamide.
- In refractory Wegener's, both infliximab and rituximab have shown some degree of promise.
- plasma exchange
- **in case of decreased conscious level with acute renal failure (with indication for dialysis) and respiratory function is failing. The first immediate step >> Endotracheal intubation and positive pressure ventilation, transfer the patient to a critical care setting (especially to protect airway with a GCS 8/15).**

**Prognosis:** median survival = 8-9 years

## Churg-Strauss syndrome (CSS)

CSS is rare an ANCA associated small-medium vessel vasculitis.

The typical picture of a patient with CCS is asthma, allergic rhinitis, mild renal impairment, microscopic haematuria, raised eosinophilic count.

**Asthma + Eosinophilia + Renal imp + Microscopic Haematuria + Nerve lesion >>> CSS**

### Features:

- Asthma
- Blood eosinophilia (e.g. **> 10%**)
- Paranasal sinusitis
- Non- fixed Pulmonary infiltrates (may be transient)
- Histological proof of vasculitis with **extravascular eosinophils by vascular biopsy.**
- Mononeuritis multiplex occurs 75% of patients (e.g. ulnar nerve palsy, foot drop) or polyneuropathy.
- pANCA positive in 60%

- **Rarely**, it can cause either an anterior or a posterior ischaemic optic neuropathy, which presents with **visual loss.**

**A diagnosis** of Churg-Strauss syndrome requires 4 of the following features:

- Asthma
- Eosinophilia greater than 10%
- Paranasal sinus abnormality
- **Non-fixed** pulmonary infiltrates visible on chest radiographs
- Mononeuropathy or polyneuropathy and
- Blood vessels biopsy with extravascular eosinophils.

**Treatment:**

Glucocorticoids, and immunosuppressant drugs (cyclophosphamide, azathioprine, MMF).

**NB:** Leukotriene receptor antagonists may precipitate the disease.

## Cryoglobulinaemia

**consumption of C4 + strongly positive rheumatoid factor → cryoglobulinaemia.**

**Immunoglobulins** which undergo **reversible precipitation at 4° C** and dissolve when warmed to 37°C. One third of cases are idiopathic.

This led to **small vessels damage** in the limbs and deposition on the wall of small vessels result in **generalized vasculitis**, which presents with a reticulated skin pattern of **microthrombosis** and areas of **gangrene.**

**Pulmonary embolism, arterial** and **venous thrombosis** are common.
**Causes of both arterial and venous thrombosis:**

- PNH.
- CRYOGLOBULINEMIA.
- BEHCET DISEASE.
- ANTIPHOSPHOLIPID SYNDROME.
- MALIGNANCY.

Recognized associations are chronic infections such as **HCV**, **SLE**, **RA** and **Sjogren's**

**Three types:**

- **Type I (25%): monoclonal**
- **Type II (25%): mixed** monoclonal and polyclonal: usually with RF
- **Type III (50%): polyclonal:** usually with RF

**Type I:**

- monoclonal - IgG or IgM
- associations: **multiple myeloma, Waldenström macroglobulinaemia**

**Type II:**

- **mixed monoclonal and polyclonal: usually with Rh .factor positive it represents the polyclonal IgG part of the immune complex.**
- associations: **HCV, lymphoma, RA, Sjogren's**

**Type III:**

- polyclonal: usually with RF
- associations: **RA, Sjogren's**

## Symptoms (if present in high concentrations):

- **Raynaud's** only seen in type I
- **Cutaneous: vascular purpura, ulcerations**
- **Arthralgia** (Non-erosive polyarthralgia associates with hepatitis C).
- **Polyneuropathy, Mononeuritis multiplex.**
- **Renal** involvement (diffuse or **Membranoproliferative** glomerulonephritis)

**Palpable purpura, arthralgia** and **myalgia** (that is, **Meltzer's triad**) seen in cryoglobulinaemia (types II/III).

## Tests:

- **High ESR**
- **Positive RF**
- **Low complement (esp. C4).**

N.B:C4 IS ALSO LOW IN ANGIODEMA.

- **Active urine sediments (Blood++, protein ++)**
- Serum cryoglobulins type II or III

In RA, RF is positive in 80% of patients, whereas in Sjogren's syndrome and cryoglobulinemia, it is prevalent in up to 90% of cases.

## Treatment:

- Of the underlying cause.
- Immunosuppression: Steroids and cyclophosphamide.
- Plasmapharesis.

**EX:** Female Pt 35 years old, arthralgia at hands, feet, wrist with Raynaud's phenomenon, tiredness, erythematous rash on both legs, high ESR 88, +ve RF, +ve ANA >>> **Cryoglobulinaemia.**

# Bechet's syndrome

Behcet's syndrome is a complex **multisystem vasculitis** disorder associated with presumed autoimmune mediated inflammation of the **arteries and veins.** It is a vasculitis of unknown pathophysiology.

The precise aetiology has yet to be elucidated however.

The classic triad of symptoms are **oral ulcers**, **genital ulcers** and **anterior uveitis.**

## Epidemiology:

- More common in the eastern Mediterranean (e.g. **Turkey, Lebanese**).
- More common in men (complicated gender distribution which varies according to country. Overall, Behcet's is considered to be more common and more severe in men).
- Tends to affect young adults (e.g. 20 - 40 years old)
- Associated in more than **60 %** with **HLA B5** and MICA6 allele (more specifically HLA B51, a split antigen of HLA B5).
- Around 30% of patients have a positive family history.

## Features:

- Classically: **1) oral ulcers 2) genital ulcers 3) anterior uveitis**
- **Thrombophlebitis** and **DVT.**
- **Arthritis** (asymmetrical, large joints like wrist and knee)
- **Neurological** involvement: severe occipital headache (e.g. **aseptic meningitis).**
- GIT: **Abd pain, diarrhoea, colitis.**
- **Erythema nodosum.**

Bechet's= Oral ulcer, Genital ulcer, Uveitis, Thrombophlebitis, Arthritis, Aseptic meningitis, Colitis.

## The International Study Group criteria for classification of Behçet's disease requires:

The presence of **recurrent oral ulceration** (minor aphthous, major aphthous or herpetiform ulceration observed by physician or patient, which have recurred at least 3 times in a 12-month period), **and TWO** of the following:

- **Recurrent genital ulceration**: aphthous ulceration or scarring, observed by physician or patient.

- **Eye lesions:** branch retinal artery occlusion (BRAO), anterior uveitis, posterior uveitis, or cells in vitreous on slit lamp examination; or retinal vasculitis observed by ophthalmologist.
- **Skin lesions:** erythema nodosum observed by physician or patient, pseudofolliculitis or papulopustular lesions; or acneiform nodules observed by the physician in post-adolescent patients not on corticosteroid treatment.
- **Positive pathergy test:** read by physician at 24-48 hours.

## Diagnosis:

- **No definitive test**
- Diagnosis based on clinical findings
- **Positive pathergy test** is the non-specific hyper-reactivity of the skin following minor trauma, and is specific to Behçet's disease. It involves intradermal injection of skin with a 20-gauge needle under sterile conditions. It is considered positive if an **erythematous sterile papule** develops within 48 hours.
- **HLA B5** is associated with ocular disease; **HLA B12** is associated with recurrent oral ulcers.

## Treatment

- **Oral ulcers and/or genital ulcers:** topical corticosteroids, topical lidocaine for pain relief
- **Arthritis or Erythema nodosum: Colchicine is the first line treatment.**
- **Ocular disease, CNS disease, and/or vasculopathy**
  - Systemic corticosteroids
  - Immunosuppressant therapy (e.g., azathioprine, infliximab, cyclosporine A, cyclophosphamide, IFN-a, methotrexate)

**NB: Conjunctivitis** is seen **rarely** and is much less common than anterior uveitis. Other ocular problems seen include scleritis, retinal vasculitis, iridocyclitis and chorioretinitis.

# Miscellaneous

**Iritis** is associated with conditions such as **Reiter's**, **Behcet's**, **psoriatic** arthropathy (about 20%) and **inflammatory bowel disease**.

The most likely organism to have been aspirated from the infected hip joint replacement prosthesis >>> **Propionibacterium acnes (PA)**: **Gram positive bacilli**, it is poorly virulent, symptoms of PA infection may occur many years after original arthropathy, it is sensitive to **penicillins**, **clindamycin** and **carbapenems**.

## Myopathies

### Features

- symmetrical muscle weakness (proximal > distal)
- common problems are rising from chair or getting out of bath
- sensation normal, reflexes normal, no fasciculation

### Causes

- inflammatory: polymyositis
- inherited: Duchenne/Becker muscular dystrophy, myotonic dystrophy
- endocrine: Cushing's, thyrotoxicosis
- alcohol

## Ehler-Danlos syndrome

Ehler-Danlos syndrome is an autosomal dominant connective tissue disorder that mostly affects type III collagen. This results in the tissue being more elastic than normal leading to joint hypermobility and increased elasticity of the skin.

### Features and complications

- elastic, fragile skin
- joint hypermobility: recurrent joint dislocation
- easy bruising
- aortic regurgitation, mitral valve prolapse and aortic dissection
- subarachnoid haemorrhage
- angioid retinal streaks

## Pseudoxanthoma elasticum

Pseudoxanthoma elasticum is an inherited condition (usually autosomal recessive*) characterised by an abnormality in elastic fibres

### Features

- retinal angioid streaks
- 'plucked chicken skin' appearance - small yellow papules on the neck, antecubital fossa and axillae
- **cardiac: mitral valve prolapse, increased risk of ischaemic heart disease**
- gastrointestinal haemorrhage

there are reports of autosomal dominant inheritance in a minority of cases

## Differential diagnoses of arthropathies associated with iron deposition in the joints: brown-stained synovial fluid.

- Haemophilia
- Haemosiderosis from recurrent haemarthrosis
- Haemochromatosis, and
- **Pigmented villonodular synovitis (PVNS).**

## Marfan's syndrome

Marfan's syndrome is an **autosomal dominant** connective tissue disorder. It is caused by a defect in the FBN1 gene on chromosome 15 that codes for the protein fibrillin-1. It affects around 1 in 3,000 people.

### Features

- tall stature with arm span to height ratio > 1.05
- high-arched palate
- arachnodactyly
- pectus excavatum
- pes planus
- scoliosis of > 20 degrees
- heart: **dilation of the aortic sinuses** (seen in 90%) which may lead to aortic aneurysm, aortic dissection, aortic regurgitation, mitral valve prolapse (75%),

- lungs: repeated pneumothoraces
- **eyes: upwards lens dislocation** (superotemporal ectopia lentis), **blue sclera**, myopia
- **dural ectasia** (ballooning of the dural sac at the lumbosacral level)

The life expectancy of patients used to be around 40-50 years. With the advent of regular echocardiography monitoring and beta-blocker/ACE-inhibitor therapy this has improved significantly over recent years. Aortic dissection and other cardiovascular problems remain the leading cause of death however.

## Langerhans cell histiocytosis

Langerhans cell histiocytosis is a rare condition associated with the abnormal proliferation of histiocytes. It typically presents in childhood with bony lesions.

### Features

- bone pain, typically in the skull or proximal femur
- cutaneous nodules
- recurrent otitis media/mastoiditis
- **tennis racket-shaped Birbeck granules on electromicroscopy**

Young girl with multiple well defined 'punched out' osteolytic lesions with scalloped edges (geographic skull) are seen in the bilateral parietal regions. The lesions have a characteristic bevelled edge

## IBD-associated arthropathy

- The history of weight loss, diarrhoea and a mono/oligo-arthropathy suggests a diagnosis of inflammatory bowel disease (IBD).
- IBD-associated arthropathy is considered a subtype of seronegative spondyloarthropathy.
- A variety of joint involvement has been described, from large joint pauciarticular arthropathy to a rheumatoid pattern polyarthropathy.
- Peripheral arthritis is generally non-erosive and the oligoarticular variant particularly may correlate with intestinal disease activity.
- Axial arthritis may include inflammatory back pain, sacroilitis, or ankylosing spondylitis and is less likely to correlate with gastrointestinal symptoms.
- mechanisms remain unclear.
- Treatment of the gastrointestinal disease is not always sufficient for control of arthritis, and biologic agents may be indicated.

The description of weight loss, diarrhoea and a mono/oligo-arthropathy suggests a diagnosis of inflammatory bowel disease. (IBD).

## McArdle's disease

### Overview

- autosomal recessive type V glycogen storage disease
- caused by myophosphorylase deficiency
- this causes decreased muscle glycogenolysis

### Features

- muscle pain and stiffness following exercise
- muscle cramps
- myoglobinuria
- low lactate levels during exercise

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# STEP UP to MRCP

3rd Edition

## Review Note For Part I & Part II

- The freshly revised and updated edition of STEP UP TO MRCP- who continued to be the reliable source for medicine - is the go-to source for current data and recommendations on diagnosis and patient management of all aspects of medicine, necessary to pass- not only MRCP, MRCPI, Masters, MDs and Board exams -but also ensure successful and safe daily practice.
- In a world of rapidly changing information and guidelines, this edition was published in response to increasing demand for a source that can successfully walk the line between the data overflow and over simplification, and I think this book did so.
- This edition includes latest and best guidelines up to those published in 2023 from NICE, ASC, AHA, RCP, AURAL, KDIGO, GOLD and other reputable and first ranked societies. It is also highly illustrated with diagrams, photos and tables that almost present in every page of this book.
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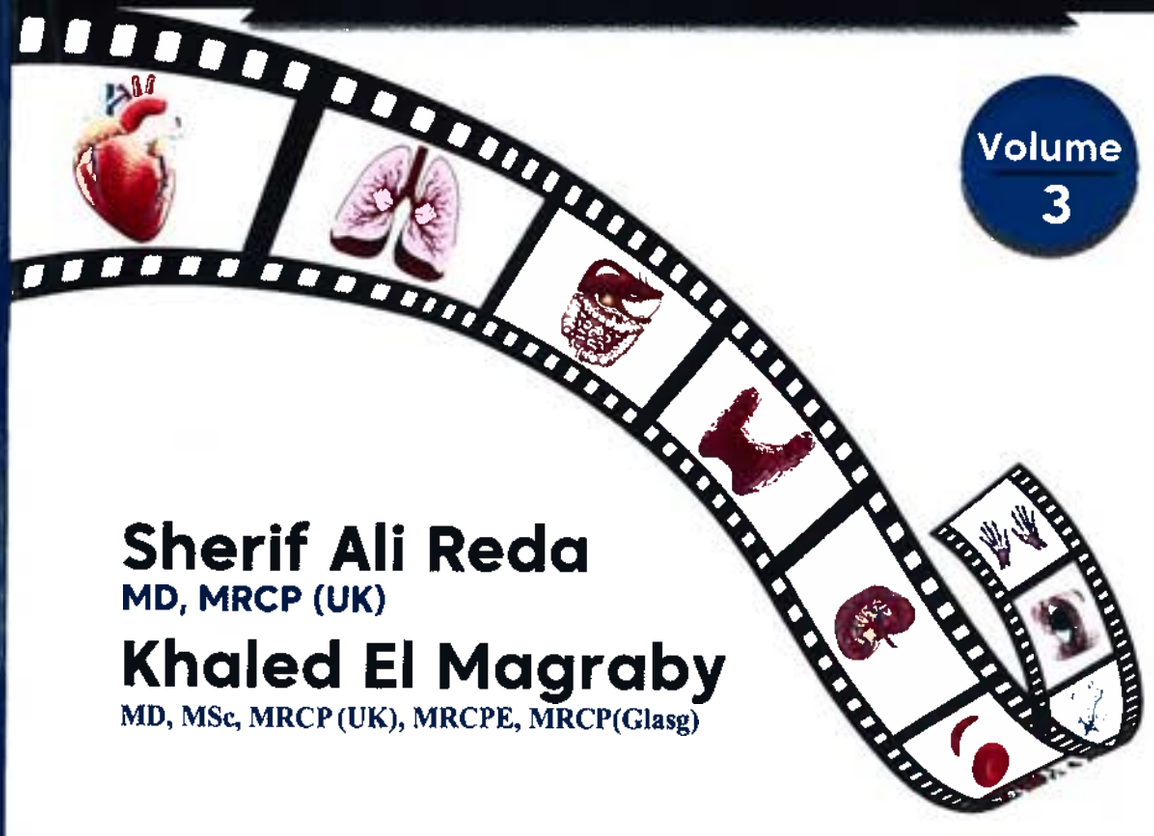

Volume 3

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VOLUME 3

EL MAGRABY & SHERIF'S

# Step Up to MRCP

Review Note for Part I & Part II

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# Step Up *to* MRCP

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**ISBN: 978-977- 86708-2-0**
Deposit Number: 11303/2023

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**Publisher**: Middle East & El Marwa for Publishing & Distribution
Cairo, Egypt
Tel. (+20) 1110150022 – (+20) 1211161255
E-mail: ar201078@gmail.com
Publishing Services Manager & Design: Abd El Hamid Abd El Ghafar
Printing Services Manager: Abd El Aleem Adel El Syed
Printed in Egypt

# PREFACE

I feel fortunate and honored to present this third edition of STEP UP TO MRCP to the community of medicine.it has been 7 years since the first edition of this book; the long interval and the increasing demand for new edition of this book- who gained a lot of trust and credibility of the medical society- was the main challenge to publish this edition.

The other challenge was to walk the line between over simplification and data overflow, in the world of internal medicine which is full of guidelines and studies.

this was the main stimulus to fill this book with diagrams, illustrations, photos, radiology material and tables, as to make it easy for everyone to pick up the needed information in an easy way for new and experienced physicians as well.

I would like to thank god for helping me to accomplish this work, and also I would like to thank the god father of this book Khalid Maghraby who invited me to contribute to this edition and helped us during completing this work.

My deepest gratitude goes to my wife Shaimaa and my kids Nada and Mohamed who tolerated me throughout this hard time. to my mother who continued to inspire and pray for me and finally to the soul of my father.

Last but not least, I would like to thank Mr,Abdelhamid the publisher and owner of middle east library ,who spent a lot of time and effort to make this book exists, attractive and in such a wonderful quality.

**S.A. Reda, MD, MRCP (UK)**
June 2023

# FORWARD

Welcome to the world of internal medicine! This medical book is the result of great effort and dedication by its author to provide you with the most updated and comprehensive knowledge of internal medicine.

The book is designed to meet the needs of every medical student, resident, and physician who is pursuing a career in internal medicine. It covers the whole spectrum of internal medicine, from the basics of pathophysiology to the most advanced treatment strategies.

The book is structured in a clear and well-organized manner.

This book is highly recommended for everyone studying internal medicine, particularly those aiming to obtain the MRCP degree. It is an invaluable resource that will help you build a strong foundation in internal medicine and prepare you for success in your medical career.

**Prof. Dr. Khaled Makboul**
Professor of internal medicine and endocrinolgy
Ain Shams University
June 2023

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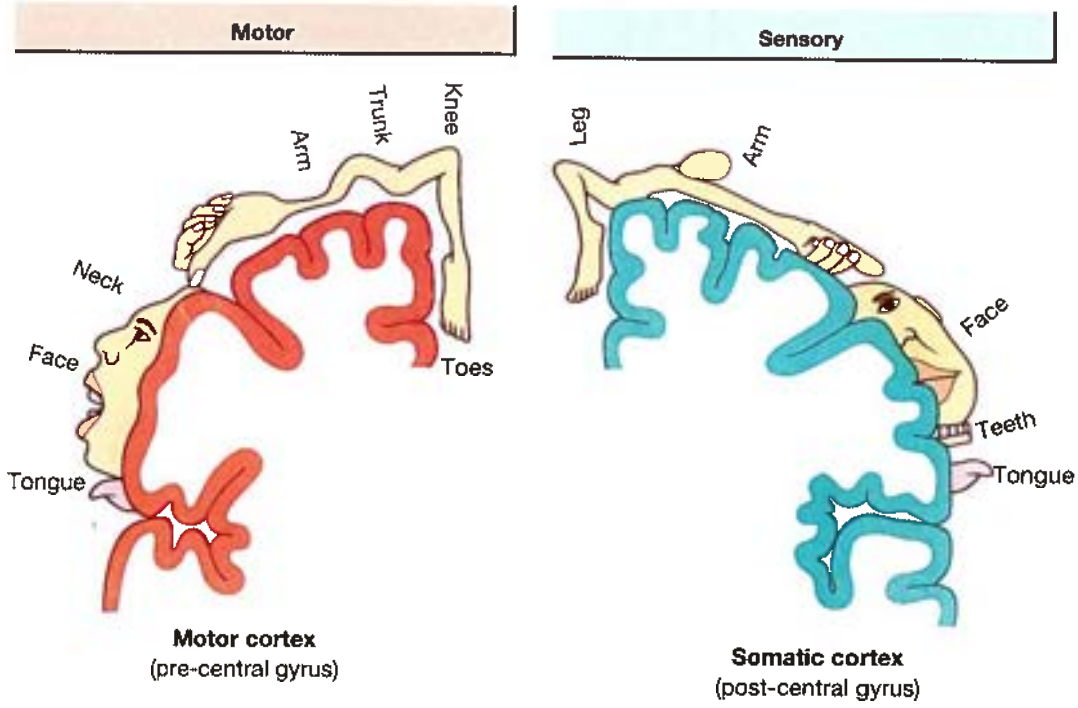
– Conus medularis syndrome, 1669
– Degenerative cervical myelopathy, 1671
– Miscellaneous, 1672
– Macroglossia, 1672
– Internuclear ophthalmoplegia, 1673
– Chronic progressive external ophthalmoplegia, 1674
– Neck lumps, 1675
– Ptosis, Miosis and Mydriasis, 1676
– Mitochondrial diseases, 1676
– DVLA: neurological disorders, 1678
– Paraneoplastic syndromes affecting nervous system, 1679
– HIV: Neurocomplications, 1680
– Pituitary tumours, 1682
– Phenytoin (Epanutin ®), 1683
– Sodium valproate (Depakin®), 1684
– Carbamazepine, 1685
– 5-HT3 antagonists, 1686
– Ethosuximide, 1687
– Topiramate, 1687
– Triptans, 1688

# Anatomy and physiology

## Neurology applied anatomy & physiology at a glance

### 1. Motor and sensory homunculi.

The motor and sensoryhomunculi illustrate the cortical areas serving each anatomical area within the pre-central (motor) and post-central (sensory) gyri.




**Motor cortex**
(pre-central gyrus)

**Somatic cortex**
(post-central gyrus)

## Cortical lobar functions

**Effects of damage**

| Lobe | Function | Cognitive/behavioural | Associated physical signs | Positive phenomena |
|---|---|---|---|---|
| **Frontal** | Personality<br>Emotional control<br>Social behaviour<br>Contralateral motor control<br>Language<br>Micturition | Disinhibition<br>Lack of initiation<br>Antisocial behaviour<br>Impaired memory<br>Expressive dysphasia<br>Incontinence | Impaired smell<br>Contralateral hemiparesis<br>Frontal release signs1 | Seizures – often nocturnal with motor activity<br>Versive head movements |
| **Parietal: dominant** | Language<br>Calculation | Dysphasia<br>Acalculia<br>Dyslexia<br>Apraxia3<br>Agnosia5 | Contralateral hemisensory loss<br>Astereognosis2<br>Agraphaesthesia4<br>Contralateral homonymous lower quadrantanopia<br>Asymmetry of optokinetic nystagmus (OKN) | Focal sensory seizures |
| **Parietal: non-dominant** | Spatial orientation<br>Constructional skills | Neglect of contralateral side<br>Spatial disorientation<br>Constructional apraxia<br>Dressing apraxia | Contralateral hemisensory loss<br>Astereognosis2<br>Agraphaesthesia4<br>Contralateral homonymous lower quadrantanopia<br>Asymmetry of OKN | Focal sensory seizures |
| **Temporal: dominant** | Auditory perception<br>Language<br>Verbal memory<br>Smell<br>Balance | Receptive aphasia<br>Dyslexia<br>Impaired verbal memory | Contralateral homonymous upper quadrantanopia | Complex hallucinations (smell, sound, vision, memory) |
| **Temporal: non-dominant** | Auditory perception<br>Melody/pitch perception<br>Non-verbal memory<br>Smell<br>Balance | Impaired non-verbal memory<br>Impaired musical skills (tonal perception) | Contralateral homonymous upper quadrantanopia | Complex hallucinations (smell, sound, vision, memory) |
| **Occipital** | Visual processing | Visual inattention<br>Visual loss<br>Visual agnosia | Homonymous hemianopia (macular sparing) | Simple visual hallucinations (e.g. phosphenes, zigzag lines) |

1Grasp reflex, palmomental response, pout response. 2Inability to determine three-dimensional shape by touch. 3Inability to perform complex movements in the presence of normal motor, sensory and cerebellar function. 4Inability to 'read' numbers or letters drawn on hand, with the eyes shut. 5Inability to recognise familiar objects, e.g. faces.

## 2-Brain lesions

The following neurological disorders/features may allow localisation of a brain lesion:

### Gross anatomy

#### Parietal lobe lesions

- sensory inattention
- apraxias
- astereognosis (tactile agnosia)
- inferior homonymous quadrantanopia
- Gerstmann's syndrome (lesion of dominant parietal): alexia, acalculia, finger agnosia and right-left disorientation

#### Occipital lobe lesions

- homonymous hemianopia (with macula sparing)
- cortical blindness
- visual agnosia

#### Temporal lobe lesion

- Wernicke's aphasia: this area 'forms' the speech before 'sending it' to Brocas area. Lesions result in word substituion, neologisms but speech remains fluent
- superior homonymous quadrantanopia
- auditory agnosia
- prosopagnosia (difficulty recognising faces)

#### Frontal lobes lesions

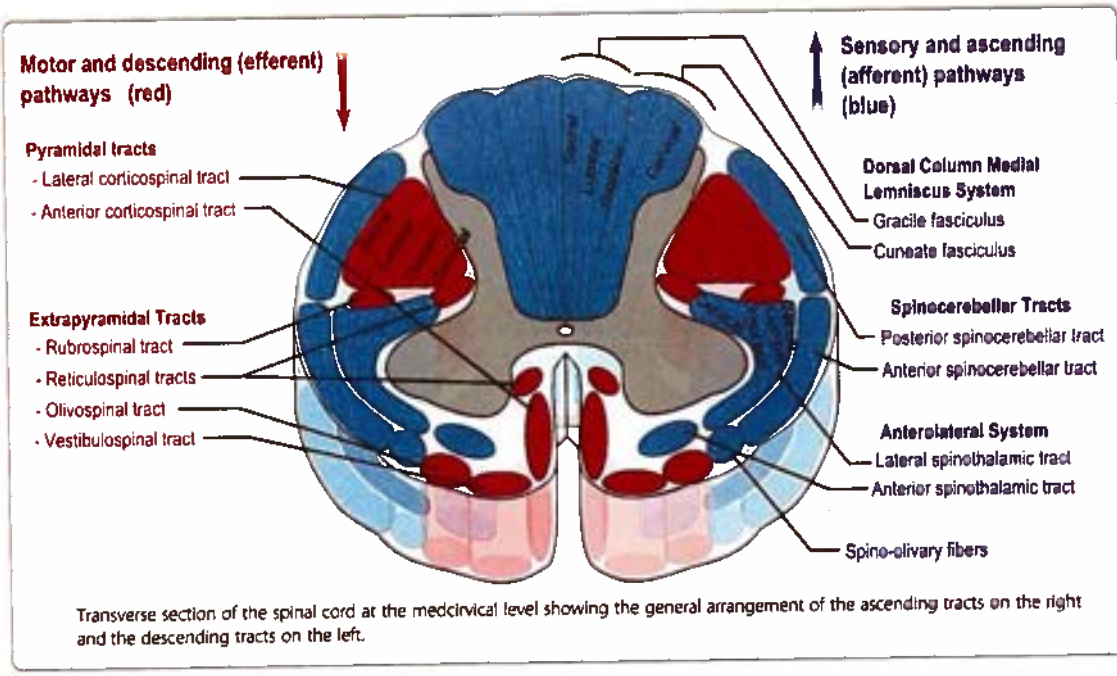
- expressive (Broca's) aphasia: located on the posterior aspect of the frontal lobe, in the inferior frontal gyrus. Speech is non-fluent, laboured, and halting
- disinhibition
- perseveration
- anosmia

inability to generate a list **Frontal lobe dementia** is a common neurodegenerative condition. It usually affects patients of **45-65 years old**. **50%** of patients presenting with **status epilepticus** (with **no** previous history of seizures) have **frontal lobe tumour**.

#### Cerebellum lesions

- midline lesions: gait and truncal ataxia
- hemisphere lesions: intention tremor, past pointing, dysdiadokinesis, nystagmus

## 3. Cross-section view of the spinal cord




Transverse section of the spinal cord at the medcirvical level showing the general arrangement of the ascending tracts on the right and the descending tracts on the left.

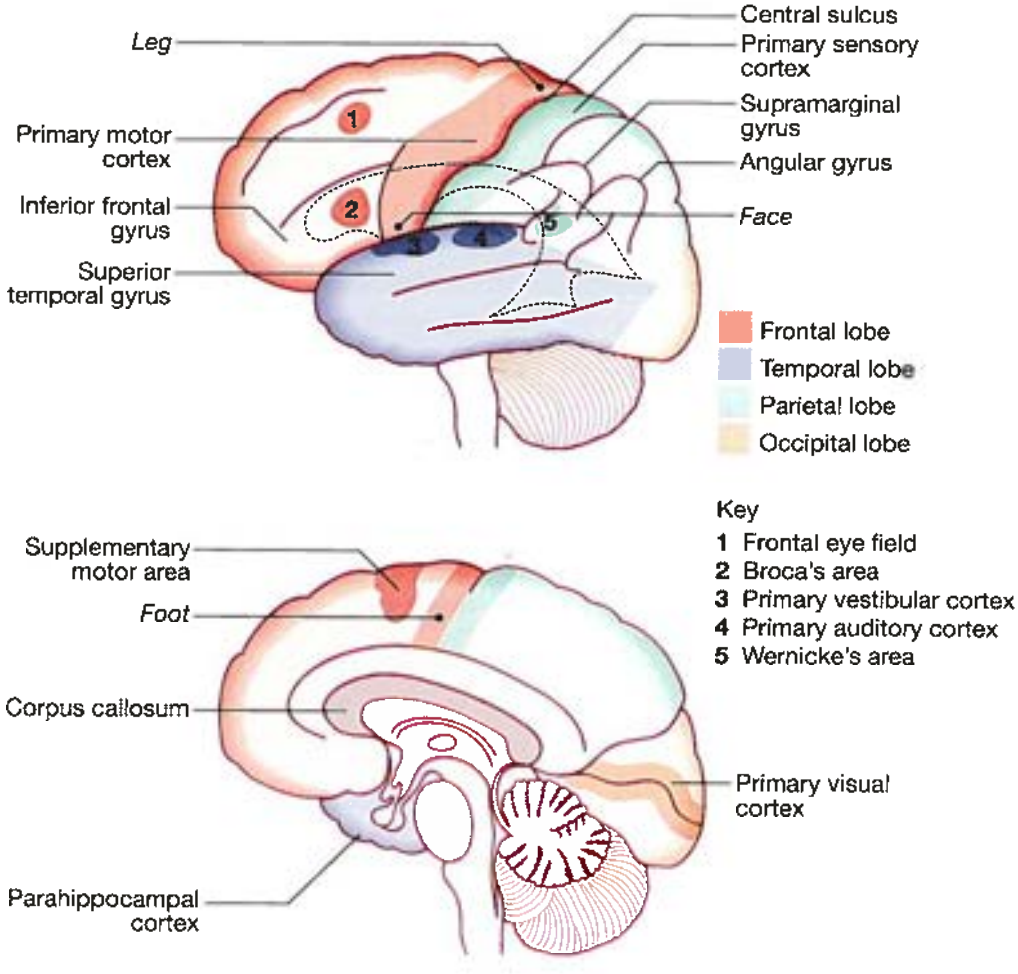
This diagram shows cross-section view of the spinal cord:

| Root values of tendon reflexes | |
|---|---|
| **Reflex** | **Root value** |
| **Arm** | |
| Biceps jerk | C5 |
| Supinator jerk | C6 |
| Triceps jerk | C7 |
| Finger jerk | C8 |
| **Leg** | |
| Knee jerk | L3/L4 |
| Ankle jerk | S1 |

## 4. Neurological emergencies

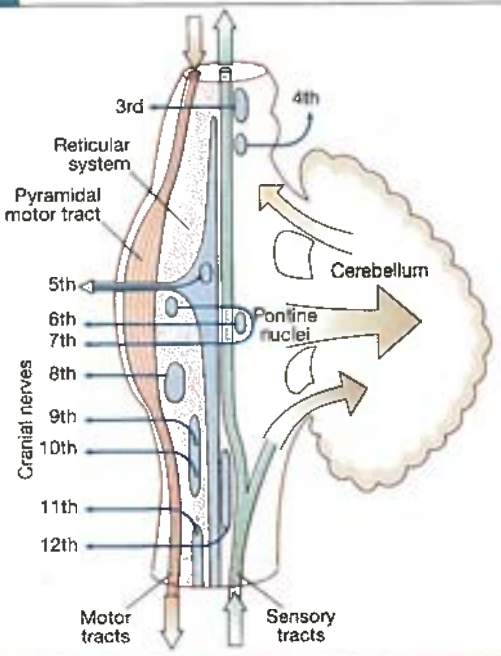
### Neurological emergencies

- Status epilepticus.
- Stroke (if thrombolysis available).
- Guillain–Barré syndrome.
- Myasthenia gravis (if bulbar and/or respiratory).
- Spinal cord compression.
- Subarachnoid haemorrhage.
- Neuroleptic malignant syndrome.



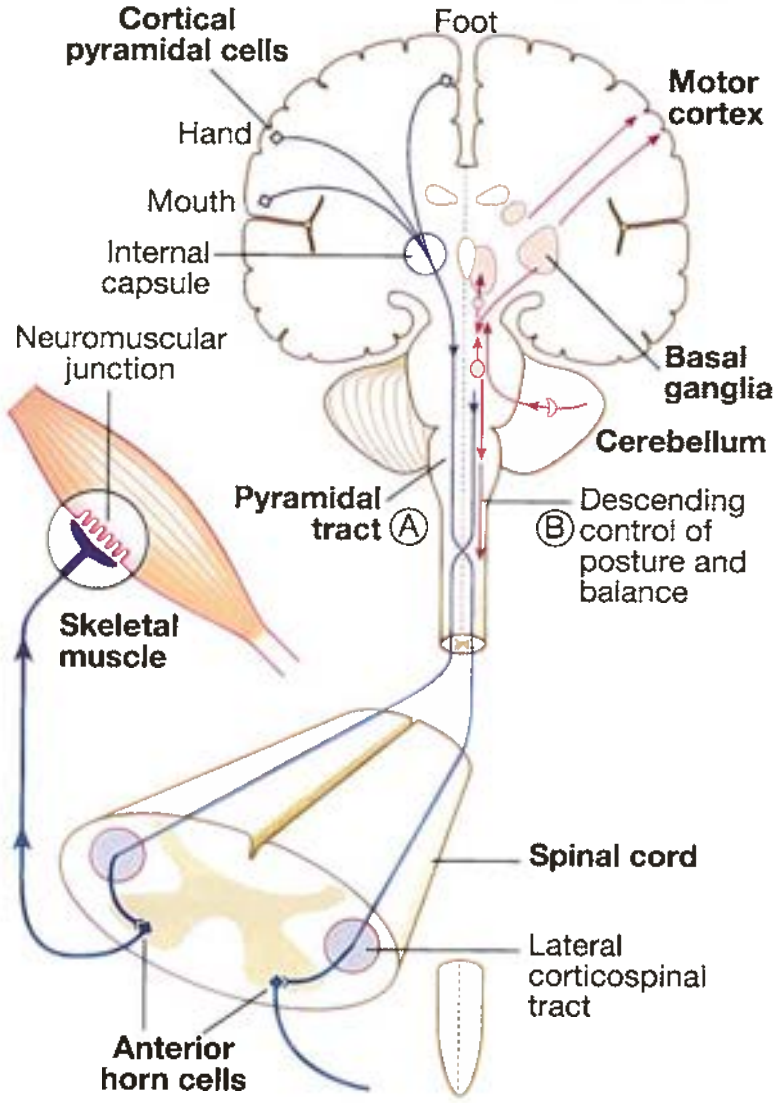

Anatomy of the cerebral cortex.

Anatomy of the brainstem.

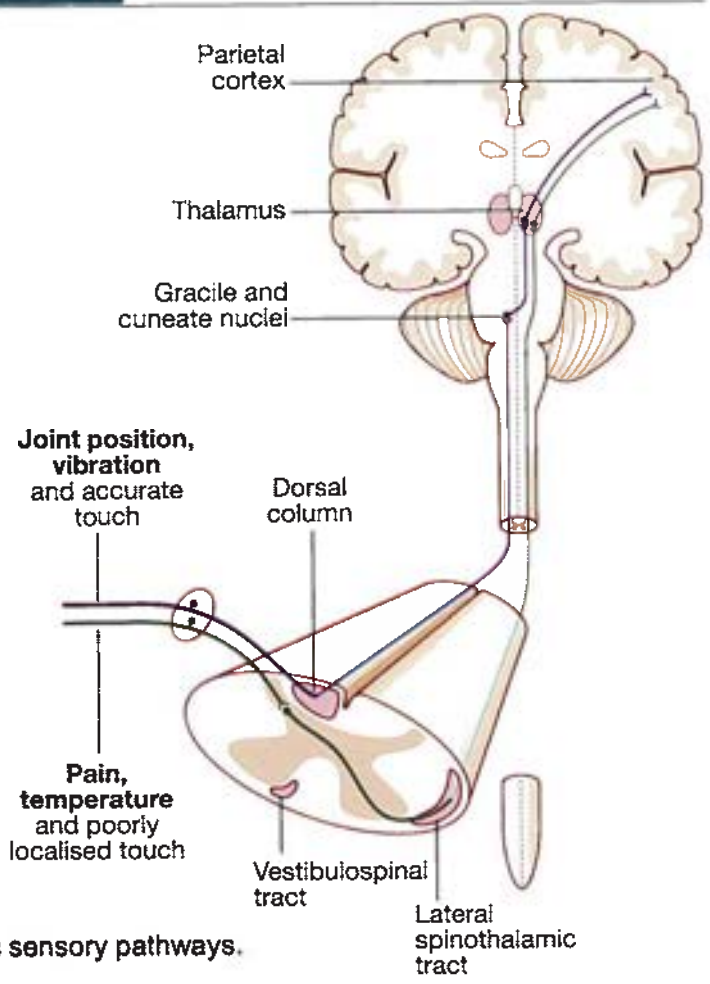



## i Major focal brainstem syndromes

| Name of syndrome | Site of lesions | Clinical features |
|---|---|---|
| Weber | Anterior cerebral peduncle (mid-brain) | Ipsilateral 3rd palsy<br>Contralateral upper motor neuron 7th palsy<br>Contralateral hemiplegia |
| Claude | Cerebral peduncle Involving red nucleus | Ipsilateral 3rd palsy<br>Contralateral cerebellar signs |
| Parinaud | Dorsal mid-brain (tectum) | Vertical gaze palsy<br>Convergence disorders<br>Convergence retraction nystagmus<br>Pupillary and lid disorders |
| Millard–Gubler | Ponto-medullary junction | Ipsilateral 6th palsy<br>Ipsilateral lower motor neuron 7th palsy<br>Contralateral hemiplegia |
| Wallenberg | Lateral medulla | Ipsilateral 5th, 9th, 10th, 11th palsy<br>Ipsilateral Horner's syndrome<br>Ipsilateral cerebellar signs<br>Contralateral spinothalamic sensory loss<br>Vestibular disturbance |




The motor system. Neurons from the motor cortex descend as the pyramidal tract in the internal capsule and cerebral peduncle to the ventral brainstem, where most cross low in the medulla **(A)**. In the spinal cord the upper motor neurons form the corticospinal tract in the lateral column before synapsing with the lower motor neurons in the anterior horns. The activity in the motor cortex is modulated by influences from the basal ganglia and cerebellum. Pathways descending from these structures control posture and balance **(B)**.




The main somatic sensory pathways.

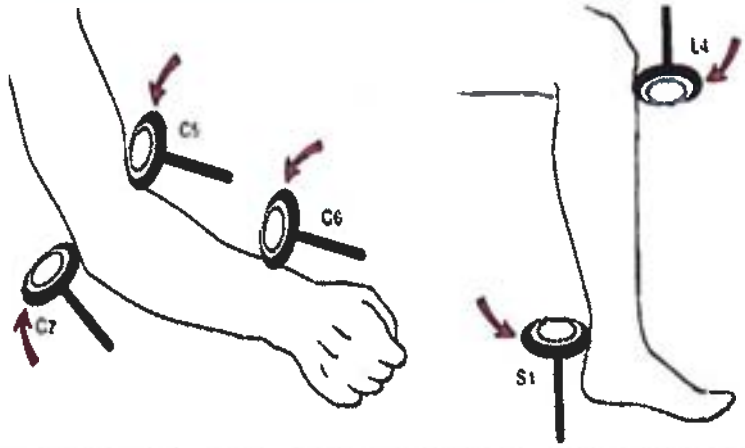
## 5. Specific areas

| Area | Associated conditions |
|---|---|
| Medial thalamus and mammillary bodies of the hypothalamus | Wernicke and Korsakoff syndrome |
| Subthalamic nucleus of the basal ganglia | Hemiballism |
| Striatum (caudate nucleus) of the basal ganglia | Huntington chorea |
| Substantia nigra of the basal ganglia | Parkinson's disease |
| Amygdala | Kluver-Bucy syndrome (hypersexuality, hyperorality, hyperphagia, visual agnosia |

| Nerve root | Landmark | Mnemonics |
|---|---|---|
| C2 | Posterior half of the skull (cap) | |
| C3 | High turtleneck shirt | |
| C4 | Low-collar shirt | |
| **C5, C6** | Thumb + index finger | Make a 6 with your L hand by touching the tip of the thumb & index finger together - C6 |
| **C7** | **Middle finger + palm of hand** | |
| C8 | Ring + little finger | |
| **T4** | **Nipples** | T4 at the Teat Pore |
| T5 | Inframammary fold | |
| **T7** | **Xiphoid process** | |
| **T10** | **Umbilicus** | BellybuT-TEN |
| T12 | Pubic bone region | |
| **L1** | **Inguinal ligament** | L for ligament, 1 for 1nguinal |
| **L4** | **Knee caps** | Down on aLL fours - L4 |
| **L5** | **Big toe**, dorsum of foot (except lateral aspect) | L5 = Largest of the 5 toes |
| **S1** | Lateral foot, **small toe** | S1 = the smallest one |
| S2, S3 | Genitalia | |

# Deep tendon reflexes: which test for which nerve root?

**C5** – Biceps
**C6** – Biceps, Brachioradialis
**C7** – Triceps
**L4** – Patellar (knee jerk) (femoral nerve mediated)
**S1** – Achilles (ankle jerk) (tibial nerve mediated)




**Inverted brachioradialis reflex (inverted supinator jerk):**

- An inverted supinator jerk, where the **biceps jerk is absent** but **generates a supinator jerk with reflex flexion of the fingers**, is indicative of **cervical myelopathy with C5/6 nerve root damage.**

**MRCPUK part 1 exam:** H/O neck & arm pain like 'electric shocks', worse on turning head + decreased sensation on the dorsal aspect of the thumb and index finger. What is the most likely underlying diagnosis?
>> C6 radiculopathy

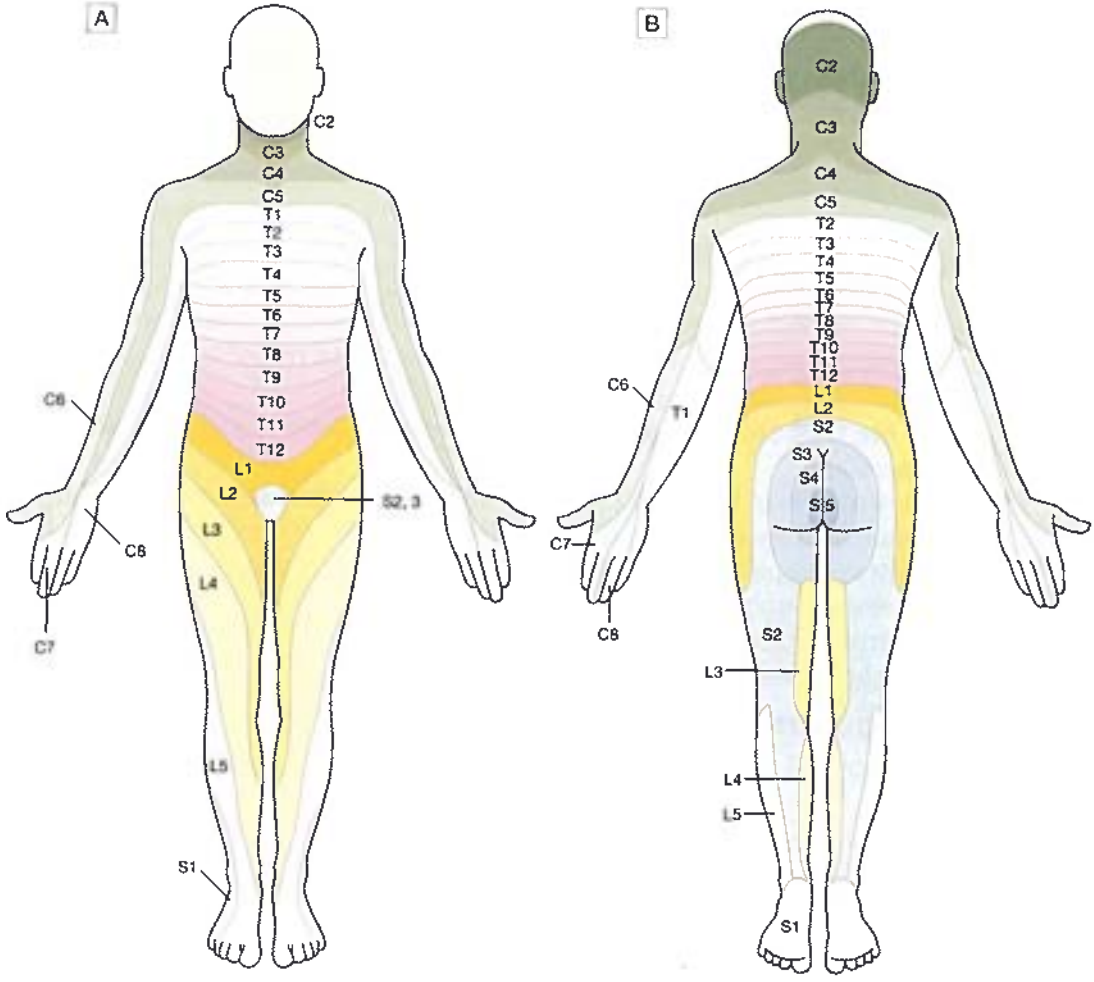
**MRCPUK part 1 exam:** Which nerve (and its nerve root) are you tested in triceps reflex?
>> Radial nerve C7

**Which spinal dermatome is responsible for the initial vague periumbilical discomfort in appendicitis?**

**mrcpuk.org SCE sample question:** H/O pain affecting buttock region and the lateral border and sole of his foot, in association with paraesthesiae of the sole on walking. What is the correct nomenclature for the nerve root from which these symptoms have arisen?
>> S1 (The S1 nerve root is mapped to the sole of the foot)

# Dermatomes

The areas supplied by specific levels of the spinal cord. These are approximations and in practice there is much overlap. The clinical utility of these dermatomes has diminished somewhat with the advent of good magnetic resonance imaging of the spinal cord but it remains important to ascertain the presence of a 'spinal level' of sensation, to remember the supply of saddle area, and to note the cervical descent of some facial spinothalamic pathways. **A** Anterior. **B** Posterior.



# General management of stroke and TIAs

This background note focuses on other issues in acute stroke management, particularly management of fluids, glycaemic control, blood pressure management, feeding assessment/management and disability scales.

## Fluid management

- As in all patients in hospital, regular assessment for fluid status must be undertaken to ensure patients remain normovolaemic
- The NICE guidelines recommend assessing the hydration of all patients with acute stroke on admission, with regular review during their stay
- Greater than 80% of patients who cannot swallow post stroke will recover within 2-4 weeks
- However, it is important to manage fluids in this immediate post-event period as hypovolaemia can worsen the ischaemic penumbra, as well as increase risk of other complications such as infection, deep vein thrombosis, constipation and delirium
- Conversely, over-hydration can also complicate matters by leading to cerebral oedema, cardiac failure and hyponatraemia, therefore it is important to regularly review fluid status in these patients
- Recommendations for management:
  - Oral hydration is preferable in all patients who are able to safely swallow
  - Intravenous hydration may be necessary otherwise, and although studies have remained contentious regarding choice of intravenous fluid, UptoDate currently recommend isotonic saline without dextrose as the agent of choice in most patients
  - Other factors to take into consideration when choosing fluid agent include electrolyte disturbances and/or cardiovascular status

## Glycaemic control

- It is important to closely monitor and control blood sugar, particularly if they are nil by mouth due to concerns regarding swallowing safety post stroke, and/or in diabetics
- Post stroke, patients with hyperglycaemia have increased mortality independent from their age and the severity of stroke
  - This is likely due to increased tissue acidosis from anaerobic metabolism, free radical generation, and increased blood brain barrier permeability post injury

- The NICE guidelines recommend maintaining a blood sugar level between 4 and 11 mmol/L in people with acute stroke
- Diabetic patients
  - It is important to provide intensive management for diabetics post acute stroke
  - The NICE guidelines suggest optimising insulin treatment using intravenous insulin and glucose infusions
  - Hypoglycaemia also needs to be managed appropriately, as alone it can cause neuronal injury as well as mimic stroke-related neurological deficits

## Blood pressure management

- Use of anti-hypertensive medications should only be used for blood pressure control in patients post ischaemic stroke if there is a hypertensive emergency with one or more of the following serious concomitant medical issues (according to the NICE guidelines):
  - Hypertensive encephalopathy
  - Hypertensive nephropathy
  - Hypertensive cardiac failure/myocardial infarction
  - Aortic dissection
  - Pre-eclampsia/eclampsia
- This is because lowering blood pressure too much can potentially compromise collateral blood flow to the affected region, and possibly hasten the time to complete and irreversible tissue infarction
- If if treatment is indicated, UptoDate recommend cautious lowering of blood pressure by approximately 15% in the first 24-hours after stroke onset
- UptoDate suggest using intravenous labetalol, nicardipine and clevidipine as first-line agents, due to the possibility for rapid and safe titration to control blood pressure
- However, in patients who are candidates for thrombolytic therapy for acute stroke, blood pressure should be reduced to 185/110mmHg or lower
  - Elevated BP can affect thrombolytic eligibility and delay treatment
  - Timely management of elevated BP is crucial when patients are otherwise eligible for intravenous thrombolysis
  - After thrombolytic therapy, UptoDate recommend ensuring that the blood pressure is stabilised and maintained at or below 180/105mmHg for at least 24 hours after treatment

## Feeding assessment and management

- All patients presenting with acute stroke must be screened for safe swallowing function prior to further oral intake, as dysphagia is common after stroke
  - This is to reduce the risk of aspiration and subsequent complications
  - This includes prior to any oral intake of food, fluids, and/or medications
- If there are any concerns regarding swallowing, the NICE guidelines recommend specialist assessment of swallowing
  - This should preferably within 24 hours of admission and not greater than 72 hours after
  - Prior to assessment is undertaken, a patient should remain nil by mouth to prevent complications
- Recommendations for patients deemed unsafe for oral intake:
  - Patients should receive nasogastric tube feeding, ideally within 24 hours of admission, unless they have had thrombolytic therapy
  - If nasogastric tube feeding is not tolerated, patients should be considered for a nasal bridle tube/gastrostomy instead
  - Medications need to be assessed to determine if formulations are available for nasogastric feeding, or if conversion to subcutaneous or intravenous forms are required
- Nutritional support may be required for patients at risk of malnutrition post stroke, whether a result from dysphagia, poor oral health or reduced ability to self-feed due to weakness or paralysis

## Disability scales

- Stroke can result in a number of complications and subsequent disability, therefore disability scales are often used as a measure of functional decline post event and subsequent improvement after medical intervention
- Disability, often measured in terms of functional status (notably, basic activities of daily living), is often the leading cause of morbidity after stroke
- After a patient is medically stabilised after a stroke, they may require transfer to a rehabilitation team for ongoing treatment depending on their level of disability
- Disability is most commonly measured using the *Barthel index* (BI), an outcome measure for stroke

  - Describes 10 tasks, and is scored according to amount of time or assistance required by the patient for each given task
  - Tasks: feeding, moving from wheelchair to bed, personal toileting, getting on/off toilet, bathing, walking on level surface, ascending/descending stairs, dressing, controlling bowels and controlling bladder
  - The total score is from 0 to 100, with 0 being completely dependent, and 100 being completely independent
- This index should be used to assess the functional status of a patient post stroke, and to monitor their improvement with ongoing rehabilitation to regain independence after the event

## Transient Ischemic Attack (TIA)

NICE published in 2019 and updated guidelines in April 2022 relating to stroke and TIA.

### Recommendations:

**Use a validated tool**, such as **FAST** (Face Arm Speech Test), outside hospital to screen people with sudden onset of neurological symptoms for a diagnosis of stroke or transient ischaemic attack (TIA).

**Exclude hypoglycaemia** in people with sudden onset of neurological symptoms as the cause of these symptoms.

For people who are admitted to the emergency department with a suspected stroke or TIA, establish the diagnosis rapidly using a validated tool, such as **ROSIER** (**R**ecognition **O**f **S**troke **I**n the **E**mergency **R**oom).

#### ROSIER score

**Exclude hypoglycemia first, then assess the following:**

| Assessment | Scoring |
|---|---|
| Loss of consciousness or syncope | - 1 point |
| Seizure activity | - 1 point |
| New, acute onset of: | |
| • asymmetric facial weakness | + 1 point |
| • asymmetric arm weakness | + 1 point |
| • asymmetric leg weakness | + 1 point |
| • speech disturbance | + 1 point |
| • visual field defect | + 1 point |

A stroke is likely if > 0.

- **Evidence showed that risk prediction scores (ABCD2 and ABCD3) used in isolation are poor at discriminating low and high risk of stroke after TIA.**
- Arranging specialist assessment less urgently for some people based on a tool with poor discriminative ability for stroke risk has the potential for harm. **Therefore, the committee agreed that risk scores should not be used.**

## Initial management of suspected and confirmed TIA

- Offer aspirin (300 mg daily), unless contraindicated, to people who have had a suspected TIA, to be started immediately.
- Refer immediately people who have had a suspected TIA for specialist assessment and investigation, to be seen within 24 hours of onset of symptoms.
- **Do not use scoring systems, such as ABCD2**, to assess risk of subsequent stroke or to inform urgency of referral for people who have had a suspected or confirmed
- TIA. Offer secondary prevention, in addition to aspirin, as soon as possible after the diagnosis of TIA is confirmed.

Imaging for people who have had a suspected TIA or acute non-disabling stroke:

## Suspected TIA

1) Do not offer CT brain scanning to people with a suspected TIA unless there is clinical suspicion of an alternative diagnosis that CT could detect. [2019]
2) After specialist assessment in the TIA clinic, consider MRI (including diffusion-weighted and blood-sensitive sequences) to determine the territory of ischaemia, or to detect haemorrhage or alternative pathologies. If MRI is done, perform it on the same day as the assessment.

## Carotid imaging

- Everyone with TIA who after specialist assessment is considered as a candidate for carotid endarterectomy should have urgent carotid imaging.

## Urgent carotid endarterectomy

**A.** Ensure that people with stable neurological symptoms from acute non-disabling stroke or TIA who have symptomatic carotid stenosis of 50% to 99% according to the NASCET (North American Symptomatic Carotid Endarterectomy Trial) are assessed and referred urgently for carotid endarterectomy to a service following current national standards (NHS England's service specification on neurointerventional services for acute ischaemic and haemorrhagic stroke) and receive best medical treatment (control of blood pressure, antiplatelet agents, cholesterol lowering through diet and drugs, lifestyle advice).

**B.** Ensure that people with stable neurological symptoms from acute non-disabling stroke or TIA who have symptomatic carotid stenosis of less than 50% according to the NASCET criteria, or less than 70% according to the European Carotid Surgery Trial (ECST) criteria:

- do not have surgery
- receive best medical treatment (control of blood pressure, antiplatelet agents, cholesterol lowering through diet and drugs, lifestyle advice.
- Ensure that carotid imaging reports clearly state which criteria (ECST or NASCET) were used when measuring the extent of carotid stenosis.

## Thrombolysis with alteplase for people with acute ischaemic stroke

Alteplase is recommended within its marketing authorisation for treating acute ischaemic stroke in adults if:

- treatment is started as soon as possible **within 4.5 hours of onset** of stroke symptoms

**and**

- intracranial haemorrhage has been excluded by appropriate imaging techniques.

Administer alteplase only within a well-organised stroke service with:

- staff trained in delivering thrombolysis and in monitoring for any complications associated with thrombolysis.
- nursing staff trained in acute stroke and thrombolysis to provide level 1 and level 2 care (seen the NHS Data Model and Dictionary on critical care level)
- immediate access to imaging and re-imaging, and staff trained to interpret the images.

(Staff in emergency departments, if appropriately trained and supported, can administer alteplase for the treatment of ischaemic stroke provided that patients can be managed within an acute stroke service with appropriate neuroradiological and stroke physician support.)

Ensure that protocols are in place for delivering and managing intravenous thrombolysis, including post-thrombolysis complications.

The National Institute of Neurological Disorders and Stroke (NINDS) issued a protocol with inclusion and exclusion criteria for tPA:

### Their inclusion criteria were:

- Age over 18
- Clinical diagnosis of acute ischaemic stroke
- Known time of onset
- CT scan consistent with diagnosis, and
- Treatment can be given within 180 minutes (though some physicians treat after this period).

### Their exclusion criteria included:

- Intracranial haemorrhage on CT scan
- Symptoms minor or improving
- Active bleeding at any site
- Gastrointestinal bleed in the last 21 days
- Major surgery in last 14 days
- History of intracranial bleed
- Serious head injury in last 3 months
- Pregnancy, or
- Active pancreatitis.

### Thrombectomy for people with acute ischaemic stroke

Offer thrombectomy as soon as possible and within 6 hours of symptom onset, together with intravenous thrombolysis (if not contraindicated and within the licensed time window), to people who have:

- acute ischaemic stroke and
- confirmed occlusion of the proximal anterior circulation demonstrated by computed

tomographic angiography (CTA) or magnetic resonance angiography (MRA) taking into account the recommended criteria.

Offer thrombectomy as soon as possible to people who were last known to be well between 6 hours and 24 hours previously (including wake-up strokes):

- who have acute ischaemic stroke and confirmed occlusion of the proximal anterior circulation demonstrated by CTA or MRA and
- if there is the potential to salvage brain tissue, as shown by imaging such as CT

perfusion or diffusion-weighted MRI sequences showing limited infarct core volume

Consider thrombectomy together with intravenous thrombolysis (where not contraindicated and within the licensed time window) as soon as possible for people last known to be well up to 24 hours previously (including wake-up strokes):

- who have acute ischaemic stroke and confirmed occlusion of the proximal posterior
- circulation (that is, basilar or posterior cerebral artery) demonstrated by CTA or MRA

**and**

- if there is the potential to salvage brain tissue, as shown by imaging such as CT

perfusion or diffusion-weighted MRI sequences showing limited infarct core volume.

People with **crescendo TIAs** (2 or more episodes in a week) should be treated as being at high risk of stroke,

**People with acute venous stroke.**

Offer people diagnosed with cerebral venous sinus thrombosis (including those with secondary cerebral haemorrhage) full-dose anticoagulation treatment (initially full-dose heparin and then warfarin . unless there are comorbidities that preclude its use.

**People with stroke associated with arterial dissection**

Offer either anticoagulants or antiplatelet agents to people who have stroke secondary to acute arterial dissection.

**People with acute ischaemic stroke associated with antiphospholipid syndrome**

Manage acute ischaemic stroke associated with antiphospholipid syndrome in the same way as acute ischaemic stroke without antiphospholipid syndrome.

### Blood pressure control for people with acute intracerebral haemorrhage

Consider rapid blood pressure lowering for people with acute intracerebral haemorrhage who do not have any of the exclusions listed and who:

- present within 6 hours of symptom onset and
- have a systolic blood pressure of between 150 and 220 mmHg.

Taking into account the risk of harm, consider rapid blood pressure lowering on a case-by-case basis for people with acute intracerebral haemorrhage who do not have any of the exclusions and who:

- present beyond 6 hours of symptom onset or
- have a systolic blood pressure greater than 220 mmHg. [2022]

When rapidly lowering blood pressure in people with acute intracerebral haemorrhage, aim to reach a systolic blood pressure of 140 mmHg or lower

while ensuring that the magnitude drop does not exceed 60 mmHg within 1 hour of starting treatment. [2022]

Do not offer rapid blood pressure lowering to people who:

- have an underlying structural cause (for example, tumour, arteriovenous malformation or aneurysm)
- have a score on the Glasgow Coma Scale of below 6
- are going to have early neurosurgery to evacuate the haematoma
- have a massive haematoma with a poor expected prognosis. [2019]

When considering blood pressure lowering in young people aged 16 or 17 with acute intracerebral haemorrhage who do not have any of the exclusions seek advice from a paediatric specialist. [2022]

### Blood pressure control for people with acute ischaemic stroke

Anti-hypertensive treatment in people with acute ischaemic stroke is recommended only if there is a hypertensive emergency with one or more of serious concomitant medical issues (see above), Blood pressure reduction to 185/110 mmHg or lower should be considered in people who are candidates for intravenous thrombolysis.

## Secondary prevention:

**NICE also published a technology appraisal in 2010 on the use of clopidogrel and dipyridamole for prevention of further OVE (occlusive vascular events).**

## Recommendations from NICE include:

- **Clopidogrel** is now recommended by NICE ahead of combination use of aspirin plus dipyridamole modified release (MR) in people who have had an ischaemic stroke.
- **Aspirin plus dipyridamole MR** is now recommended after an ischaemic stroke **only if clopidogrel is** contraindicated or not tolerated, but treatment is **no longer limited to 2 years' duration (i.e. it will be lifelong).**
- **Dipyridamole MR alone** is recommended after an ischaemic stroke only if aspirin or clopidogrel are contraindicated or not tolerated, again with **no limit on duration of treatment. (i.e. it will be lifelong).**

**Secondary prevention of OVE:**

- **Clopidogrel**
- Aspirin plus dipyridamole MR
- Dipyridamole MR alone

Dipyridamole is not to be used in acute phase.

**EX**: Pt with ischemic stroke: at discharge from hospital after 14 days >> he should receive: (**Clopidogrel** + **Statin If** the cholesterol is **> 3.5).**

# Carotid artery dissection

The **two** commonest causes of **young onset stroke** (**less than 40 years**) are **cardio embolism** and **carotid artery dissection.**

**75%** of carotid dissections affect the **internal carotid artery** (that is, **extracranially**), and may be related to neck trauma or manipulation, although the cause is often difficult to identify.

The classic **triad** of symptoms of carotid dissection are:

- **Unilateral (ipsilateral) headache**
- **Ipsilateral Horner's** syndrome and
- **Contralateral hemisphere** signs (aphasia, neglect, visual disturbance, and hemiparesis).

**Headache** is commonly **ipsilateral** to the **side** of the **carotid dissection**, and recurrence of the headache suggests extension or recurrence of the dissection.

The Horner's syndrome is caused by compression of the ascending sympathetic supply within the carotid sheath, and results in ptosis and miosis.

Anhydrosis is classically not present as the sympathetic supply to the sweat glands is along the external carotid plexus and is therefore spared.

**Ischaemic** neurological features (**transient** or completed **strokes**) are found in **30-80%** of patients presenting with carotid artery dissection.

Diagnosed by **Contrast arteriography** of **the neck vessels**

Management is aimed at preventing cerebral infarction, and is similar to that of acute stroke. Stenting can be used if there is ongoing ischaemia.

**EX:** A 21-year-old female presented with a sudden onset of **left sided head and neck pain.**

24 hours later she presents with **sudden onset of right hemiparesis**, facial weakness and **homonymous hemianopia** and **left Horner's syndrome**.

A CT brain showed **a left middle cerebral artery territory infarction**.

The most likely diagnosis? **Lt Carotid artery dissection**

**NB: Migrainous stroke** usually affects the **posterior** circulation (posterior cerebral artery territory is the commonest).

**NB:** A thrombotic event resulting from **cardio embolism** or **antiphospholipid syndrome** would usually **only** affect **intracranial** vessels and therefore a **Horner's** syndrome would be **unusual**.

## Neurosurgical intervention in acute ischaemic stroke:

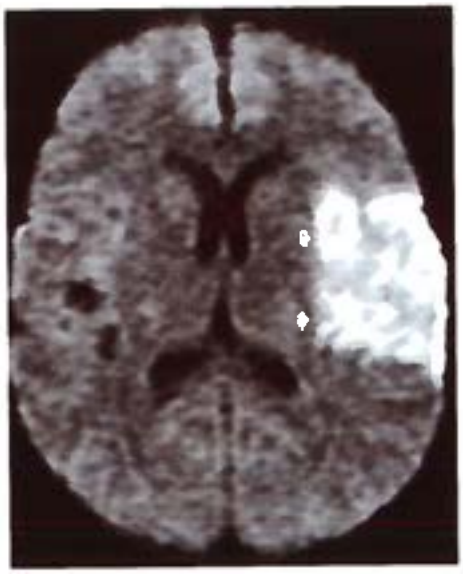
1) Patients who are **under 60 years** of age with **large cerebral infarctions** arising in the **MCA territory** should be considered for **decompressive hemicraniectomy** which is removing part of the skull in order to reduce ICP and should be carried out within 48 hours of the index event.
2) A **massive cerebellar infarction** or evidence of **hydrocephalus** or **brainstem compression**.

# Stroke by anatomy

| Site of the lesion | Associated effects |
|---|---|
| Anterior cerebral artery (ACA) | -Contralateral hemiparesis and sensory loss, lower extremity > upper.<br>-Disconnection syndrome (Akinetic mute patient). |
| Middle cerebral artery (MCA) | -Contralateral hemiparesis and sensory loss, upper extremity > lower.<br>-Contralateral homonymous hemianopia.<br>-Aphasia (Wernicke's).<br>-Gaze abnormalities. |
| Posterior cerebral artery (PCA) | - Pure hemisensory loss<br>- Contralateral homonymous hemianopia with macular sparing.<br>-Visual agnosia.<br>- Disorders of reading (alexia, dyslexia)<br>- Disconnection syndrome. |
| Weber's syndrome (branches of the PCA that supply the midbrain) | -Ipsilateral CN III palsy.<br>-Contralateral weakness. |
| Posterior inferior cerebellar artery (= lateral medullary syndrome), (=Wallenberg syndrome) | - Ipsilateral cerebellar: Ataxia, nystagmus.<br>- Ipsilateral signs of Horner's syndrome.<br>- Ipsilateral loss of corneal reflex<br>- Ipsilateral facial loss of pinprick sensation<br>- **Contralateral** signs of **spinothalamic** sensory loss of the limb/torso **pain and temperature loss.** |
| Anterior inferior cerebellar artery (lateral pontine syndrome) | Symptoms are similar to Wallenberg's (see above), but add:<br>Ipsilateral: facial paralysis and deafness |
| Pontine | -6 th nerve palsy: horizontal gaze palsy.<br>-7 th nerve palsy<br>-Contralateral hemiparesis. |
| Retinal/ophthalmic artery | Amaurosis fugax |
| **B**asilar artery | **'Locked-in' syndrome**: Pt is awake but is unable to respond in anyway except by vertical gaze and blinking (lesion is in ventral **pons**). |

## Lacunar strokes:

- Present with either isolated hemiparesis, hemisensory loss or hemiparesis with limb ataxia.
- Strong association with HTN
- Common sites include the basal ganglia, thalamus and internal capsule.



Acute left middle cerebral artery infarct on MRI of a 65-year-old hypertensive man. The MRI demonstrates increased signal intensity (arrows). Abnormalities in MRI occur before those seen on CT during ischemic strokes

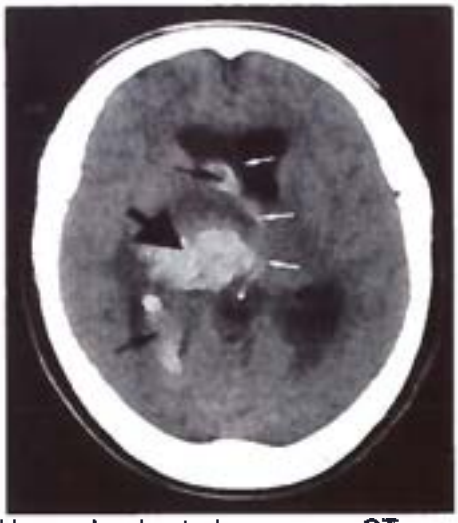
Noncontrast CT image of a subacute left middle cerebral artery infarct (arrows). This was done 2 weeks after the stroke in the same patient as previous figure. CT findings occur later than MRI findings in ischemic strokes.

image of right middle cerebral artery infarct; the hypodense (darker) area (arrows) indicates the infarct. The midline structures are shifted to the left.

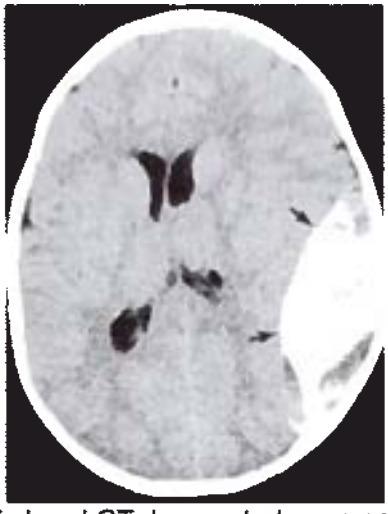
Hemorrhagic stroke. CT image demonstrates bleeding in the right basal ganglia (large black arrow) and into the ventricles (small black arrows). Blood appears white on the CT scan. The white arrows illustrate midline shift.

CT scan of an acute subdural hematoma (arrow) seen as a hyperdense clot with an irregular border. There is a midline shift from the mass effect of the accumulated blood.

CT scan of chronic bilateral subdural hematomas. As subdural hematomas age, these become iso-dense gray and then hypodense (darker gray to black) compared to the brain. Some resolving blood is still visible on the left (arrows).



Hemorrhagic stroke seen on CT. The CT image demonstrates bleeding in the right basal ganglia (large black arrow) into the ventricles (small black arrows) with midline shift (white arrows).



This head CT demonstrates an epidural hematoma, with the typical biconvex appearance (arrows). Note how the biconvex appearance resembles the lens of an eye.

A subarachnoid hemorrhage appears as areas of high density (more white like bone rather than the darker gray of brain tissue) in the subarachnoid space (arrows).

# CADASIL

## Overview

- Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL)
- rare cause of multi-infarct dementia
- patients often present with migraine.
- A family history is almost always present, as it is an autosomal dominant condition, **located to chromosome 19**.
- the most common genetic form of vascular dementia.

## Features

- **What is the pathophysiology of this condition?**
  - **NOTCH3 mutation**

## Diagnosis

- Characteristic MRI changes include T2 weighted hyperintensity of the periventricular white matter.
- **DNA testing** for the **notch-3 gene mutation** confirms the diagnosis.

## Treatment

- the **oral contraceptive pill should be stopped**, given its association with stroke in migraine.

# Lateral medullary syndrome (Wallenberg's syndrome)

Again it occurs following occlusion of the **posterior inferior cerebellar artery (PICA)**.

**Cerebellar features**: Ataxia and nystagmus.

**Brainstem features:**

- **Ipsilateral**: dysphagia, facial numbness, cranial nerve palsy e.g. **Horner's**
- **Contralateral**: **limb sensory loss** (pyramidal tract signs).
- Weber's syndrome
  - psilateral III palsy
  - contralateral weakness

**Lateral medullary syndrome >> PICA lesion >> Ipsilateral Cerebellar signs + Ipsilateral Horner's + Contralateral limb sensory loss.**

## Glasgow coma scale (GCS)

| Eye opening (4) | Verbal response (5) | Motor response (6) |
|---|---|---|
| Spontaneously | Orientated | Obeys verbal commands |
| To speech | Disorientated | Localises painful stimuli |
| To painful stimulus | Inappropriate words | Withdrawal to pain |
| No response | Incomprehensible sounds | Flexion to pain |
| | No response | Extension to pain |
| | | No response |

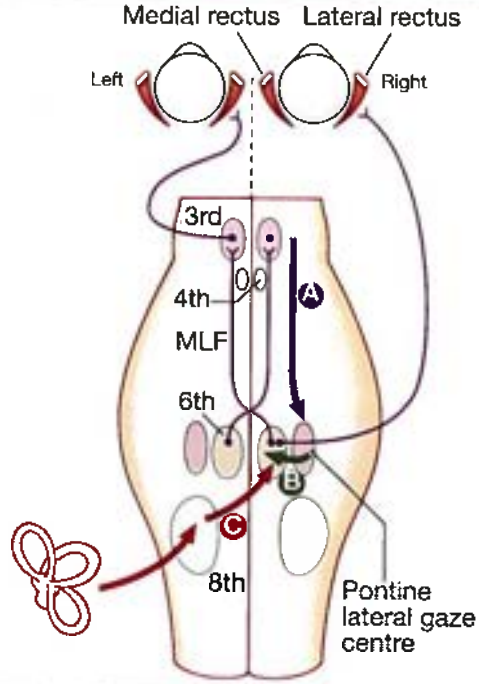
### Spaces:

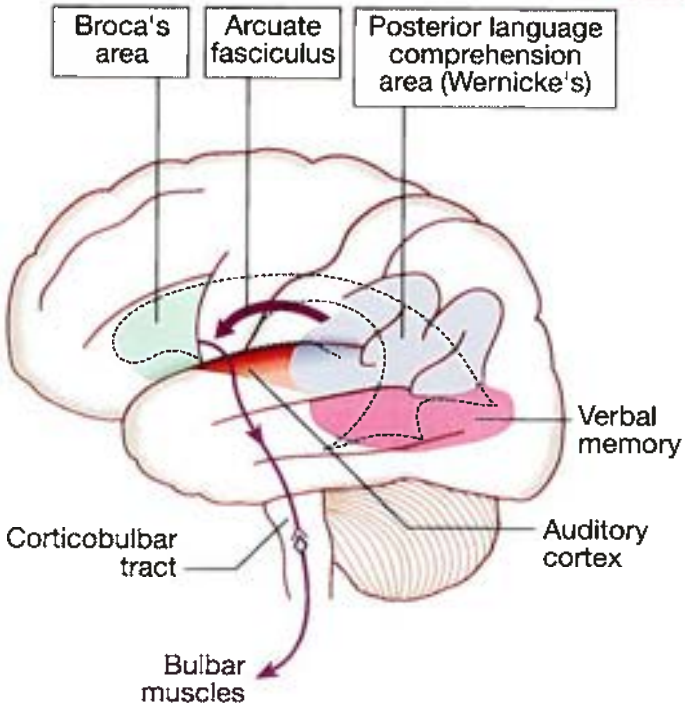
- **Subarachnoid space** is in between the arachnoid mater and the pia mater. Vascular malformations and aneurysms typically bleed in the subarachnoid space e.g. CT shows blood in the Sylvain fissure.
- **Subdural** refers to the area between the dura and the arachnoid.
- **Epidural** is between the skull and the dura.
- **Subgaleal** is a potential space between the skull and the scalp aponeurosis.
- **Subcortical** is in the white matter of the brain below the cortex.

### Lesions:

- **FTD** (fronto-temporal dementia) appears to begin in the **orbitofrontal cortex** and **anterior cingulate regions** of the frontal lobes, along with the anterior insula.
- Damage to the **hippocampus** and **parahippocampus** results in memory problems and has early involvement in **Alzheimer's** disease.
- The **corpus callosum** can be involved in **multiple sclerosis** where so-called Dawson's fingers can be seen.
- **Prefrontal cortex** damage can result in disinhibition and problems with social interaction and judgement and has been implicated in **schizophrenia**.

Control of conjugate eye movements. Downward projections pass from the cortex to the pontine lateral gaze centre (A). The pontine gaze centre projects to the 6th cranial nerve nucleus (B), which innervates the ipsilateral lateral rectus and projects to the contralateral 3rd nerve nucleus (and hence medial rectus) via the medial longitudinal fasciculus (MLF). Tonic inputs from the vestibular apparatus (C) project to the contralateral 6th nerve nucleus via the vestibular nuclei




Areas of the cerebral cortex involved in the generation of spoken language.

## Subclavian Steal Syndrome

- It is associated with retrograde flow in the vertebral artery due to proximal subclavian artery stenosis.
- **Neurological symptoms** are precipitated by vigorous exercise with the arm above the head, such as painting a wall.
- **Diagnosis** is often confused with TIA or epilepsy.
- **Duplex US and MRA** are the investigations of choice.
- **Treatment:** Endarterectomy and stenting.

## Intracranial venous thrombosis

### Overview:

- Can cause cerebral infarction, much less common than arterial causes.
- **50%** of patients have **isolated sagittal sinus thrombosis** - the remainder have coexistent lateral sinus thrombosis and cavernous sinus thrombosis.
- Venous sinus thrombosis is associated with the **oral contraceptive pill**, the **post-partum period** and **other hypercoagulable states**.

### Features:

- Headache (may be sudden onset)
- Nausea & vomiting
- reduced consciousness

### Sagittal sinus thrombosis:

- May present with seizures and hemiplegia
- Parasagittal biparietal or bifrontal haemorrhagic infarctions are sometimes seen.

### Cavernous sinus thrombosis:

- Other causes of cavernous sinus syndrome: local infection (e.g. sinusitis), neoplasia, trauma
- **Periorbital oedema.**
- **Ophthalmoplegia**: **6th** nerve damage typically occurs before **3rd** & $4^{th}$.
- **Trigeminal nerve (5th)** involvement may lead to hyperaesthesia of upper face and eye pain.
- **Central retinal vein thrombosis.**

**Lateral sinus thrombosis:** 6th and 7th cranial nerve palsies.

CT with contrast demonstrating a **superior sagittal sinus thrombosis** showing the typical empty delta sign. Look at the 'bottom' of the scan for the triangular shaped dural sinus. This should normally be white due to it being filled with contrast. The empty delta sign occurs when the thrombus fails to enhance within the dural sinus and is outlined by enhanced collateral channels in the falx. This sign is seen in only about 25%-30% of cases but is highly diagnostic for sagittal sinus thrombosis

**EX:** A 28-year-old female, **3 days post-partum**, develops **severe headache** associated with **seizures**.
During her pregnancy her BP had been mildly elevated in the third trimester.
On examination, she had a GCS of 15 but was slightly **confused** and drowsy. Her temperature was 37.5°C, she had mild nuchal rigidity but neurological examination was otherwise normal.
The most likely diagnosis >>> **Cortical vein thrombosis >>>** Do **MRV.**

**Treatment:** is Anti-**coagulation**

**NB:**

- **Post-partum period** is a risk factor of **cortical vein** and **sinus thrombosis**.
- It typically presents with **headache**, **seizures** and **focal** neurological deficit **2 to 3 weeks postpartum** (but is also seen earlier).
- Although eclampsia would be in the differential diagnosis in this case, **nuchal rigidity** is **not** a typical feature which points more to the direction of cortical vein thrombosis.
- The **eclampsia** seizures can in fact occur antepartum, intrapartum, or postpartum. If a seizure does occur **postpartum**, it usually occurs **within the first 24 hours after delivery.**
- Other clinical presentations include an idiopathic intracranial hypertension (BIH) type of picture (papilledema, visual disturbances and headaches) or a subacute encephalopathic picture. Thrombophilia screen should be performed.

**EX**: A 30-year-old lady presented with **headache** which she first noticed as she was picking up **her 5-week-old baby**.

On admission she was **unable to tolerate the lights** and complained of feeling sick. Fundoscopy showed **bilateral papilledema**, and she was complaining that she was unable to see on her left side. **CT head showed a small right occipital bleed >>> venous sinus thrombosis >>> Treatment: urgent LMWH.**
This lady has developed a **venous sinus thrombosis peri-partum** resulting in symptoms of headache, photophobia and vomiting.

The small occipital bleed has resulted from **venous congestion** and she needs urgent Treatment with LWMH to prevent clot propagation and further complications.

This woman's symptoms are not as a result of a subarachnoid aneurysm, so aneurysm coiling and nimodipine are not appropriate.

A lumbar puncture is not appropriate as she does not have idiopathic intracranial hypertension.

She does not have migraine and so a triptan is not appropriate

## Head injury

NICE has strict and clear guidance regarding which adult patients are safe to discharge and which need further CT head imaging.

The former group are also divided into two further cohorts, those who require an immediate CT head and those requiring CT head within 8 hours of injury:

### CT head immediately:

- GCS < 13 on initial assessment.
- **GCS < 15 at 2 hours post-injury.**
- Suspected open or depressed skull fracture.
- Any sign of basal skull fracture (haemotympanum, 'panda' eyes, and CSF leakage from the ear or nose, Battle's sign).
- Post-traumatic seizure.
- Focal neurological deficit.
- More than 1 episode of vomiting

## CT head scan within 8 hours of the head injury:

**For adults with any of the following risk factors who have experienced some loss of consciousness or amnesia since the injury:**

- Age 65 years or older.
- Any history of bleeding or clotting disorders.
- Dangerous mechanism of injury (a pedestrian or cyclist struck by a motor vehicle, an occupant ejected from a motor vehicle or a fall from a height of greater than 1 metre or 5 stairs).
- More than 30 minutes' retrograde amnesia of events immediately before the head injury.

**N.B**: If a patient is on **warfarin** who have sustained a head injury with no other indications for a CT head, **perform a CT head scan within 8 hours** of the injury.

## Types of traumatic brain injury

### Basics:

- Primary brain injury may be focal (contusion/haematoma) or diffuse (diffuse axonal injury).
- Diffuse axonal injury occurs as a result of mechanical shearing following deceleration, causing disruption and tearing of axons.
- Intra-cranial haematomas can be extradural, subdural or intra-cerebral, while contusions may occur adjacent to (coup) or contralateral (contre-coup) to the side of impact.
- Secondary brain injury occurs when cerebral oedema, ischaemia, infection, tonsillar or tentorial herniation exacerbates the original injury.
- The **normal cerebral auto regulatory** processes are disrupted following trauma rendering the brain more susceptible to blood flow changes and hypoxia.
- The **Cushings reflex** (**hypertension and bradycardia**) often occurs late and is usually a pre terminal event.

**EX**: A 14-year-old boy bangs heads with an opponent during an unofficial football game. He is knocked out for 30 seconds and is amnesic for the event. He recovers quickly and continues playing.
Two hours later he complains of headache, begins vomiting then loses consciousness >>> **Extra-Dural haematoma >>> CT brain.**

## Comparison of intracranial Hemorrhage

| Feature | Subarachnoid | Subdural | Extradural |
|---|---|---|---|
| **Location** | The inner most layer around the brain tissue | Between the dura mater and arachnoid mater | The outermost layer, between the skull and dura mater |
| **Mechanism** | Usually due to rupture of a blood vessel (e.g. berry aneurysm or AVM). Pain typically felt at the back of the head | Usually due to trauma causing damage to one of the bridging veins. may be minor and could be many months ago. Can be acute or chronic | Due to direct moderate/ severe head trauma. Typically around the eye, causing fracture of the temporal or parietal bone, resulting in laceration of the middle meningeal artery and / or vein |
| **Pain** | Sudden onset painful, | Possible dull headache | Likely, and often severe, but not sudden onset |
| **Consciousness** | May become impaired quickly - if So, a very bad prognostic indicator | Fluctuates, often over weeks or even months | Classically, an initial lucid period, followed by impaired consciousness |
| **Neurological signs** | May be present; are a poor prognostic indicator | Often insidious. May involve memory impairment, epilepsy, drowsiness, dizziness. Often occur weeks / months after injury | Typically after a lucid period, severe headache, impaired consciousness. Vomiting, seizures, drowsiness, confusion, and later, coma. |
| **Investigations** | CT- should show irregular shaped bleed. If absent, and still suspicious. do LP to confirm (blood in CSF, CSF turn yellow when left to stand - xanthochromia) | CT / MRI - classically shows a crescent of blood around the brain tissue, and midline shift | CT / MRI - described as a lens Shaped lesion - meaning it is biconvex. LP is contraindicated! X-ray may show skull fracture |
| **Management** | If few symptoms, surgical clipping of platinum coiling of aneurysm, or if AVM then balloon therapy and stenting are beneficial. Give Nimodipine to reduce risk of vasospasm (and ↑ Survival) as long as BP can be maintained. | Burr hole or craniotomy | Surgery to evacuate blood and ligate bleeding vessels |

# Subarachnoid hemorrhage (SAH)

- A subarachnoid haemorrhage (SAH) is an intracranial haemorrhage that is defined as the presence of blood within the subarachnoid space, i.e. deep to the subarachnoid layer of the meninges.
- The most common cause of SAH is head injury and this is called traumatic SAH.
- In the absence of trauma, SAH is termed spontaneous SAH.
- The rest of this note focuses on spontaneous SAH.

## Causes of spontaneous SAH include:

- 85% are due to rupture of berry aneurysms
- Conditions associated with berry aneurysms **include adult polycystic kidney disease**, Ehlers-Danlos syndrome and coarctation of the aorta
- Arteriovenous malformation
- Pituitary apoplexy
- Arterial dissection
- Mycotic (infective) aneurysms
- Peri- mesencephalic (an idiopathic venous bleed)
- Trauma.
- Tumors.

## Classical presenting features include:

- Headache: typically, sudden-onset ('thunderclap' or 'baseball bat'), severe ('worst of my life') and occipital
- Nausea and vomiting
- Meningism (photophobia, neck stiffness)
- Coma
- Seizures
- Sudden death
- ECG changes including ST elevation may be seen

## Investigations

### CT head

- Acute blood (hyperdense / bright on CT) is typically distributed in the basal cisterns, sulci and in severe cases the ventricular system.
- CT is negative for SAH (no blood seen) in 7% of cases.

### LP

- **Used to confirm SAH if CT is negative.**

- LP is performed at least **12 hours** following the onset of symptoms to allow the development of **xanthochromia (the result of red blood cell breakdown).**
- Xanthochromia helps to distinguish true SAH from a 'traumatic tap' (blood introduced by the LP procedure).
- As well as xanthochromia, CSF findings consistent with subarachnoid haemorrhage include a normal or raised opening pressure

**Referral to neurosurgery to be made as soon as SAH is confirmed**

After spontaneous SAH is confirmed, the aim of investigation is to identify a causative pathology that needs urgent treatment:

- CT intracranial angiogram (to identify a vascular lesion e.g. aneurysm or AVM)
- +/- digital subtraction angiogram (catheter angiogram)

## Management:

- The treatment in spontaneous SAH is in accordance with the causative pathology
- Intracranial aneurysms are at risk of rebleeding and therefore require prompt intervention, preferably within 24 hours
- Most intracranial aneurysms are now treated with a coil by interventional neuroradiologists, but a minority require a craniotomy and clipping by a neurosurgeon
- Until the aneurysm is treated, the patient should be kept on strict bed rest, well-controlled blood pressure and should avoid straining in order to prevent a re-bleed of the aneurysm
- Vasospasm is prevented using a 21-day course of nimodipine (a calcium channel inhibitor targeting the brain vasculature) and treated with hypervolemia, induced-hypertension and haemodilution**
- Hydrocephalus is temporarily treated with an external ventricular drain (CSF diverted into a bag at the bedside) or, if required, a long-term ventriculo-peritoneal shunt

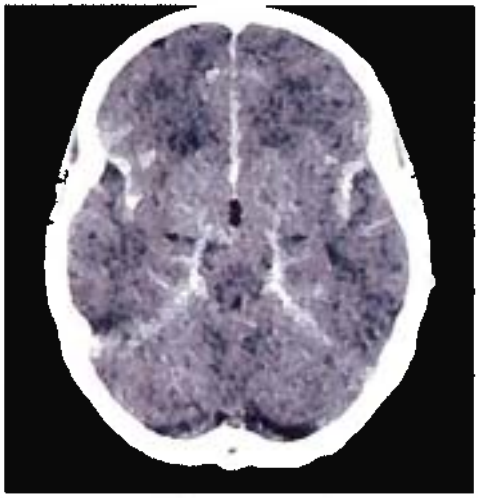
## Complications of aneurysmal SAH:

- Re-bleeding
  - happens in around 10% of cases and most common in the first 12 hours
  - if rebleeding is suspected (e.g. sudden worsening of neurological symptoms) then a repeat CT should be arranged
  - associated with a high mortality (up to 70%)

- Vasospasm (also termed delayed cerebral ischaemia), typically 7-14 days after onset
- Hyponatremia (most typically due to syndrome inappropriate anti-diuretic hormone (**SIADH**)
- Seizures
- Hydrocephalus
- Death

## Important predictive factors in SAH:

- conscious level on admission
- age
- amount of blood visible on CT head



**CT image shows diffuse subarachnoid haemorrhage in all basal cisterns, bilateral sylvian fissures and the inter-hemispheric fissure. This case demonstrates the typical distribution that takes the blood into the subarachnoid space in a subarachnoid hemorrhage.**

*this may be secondary to either autonomic neural stimulation from the hypothalamus or elevated levels of circulating catecholamines

the way nimodipine works in subarachnoid haemorrhage is not fully understood. It has been previously postulated that it reduces cerebral vasospasm (hence maintaining cerebral perfusion) but this has not been demonstrated in studies

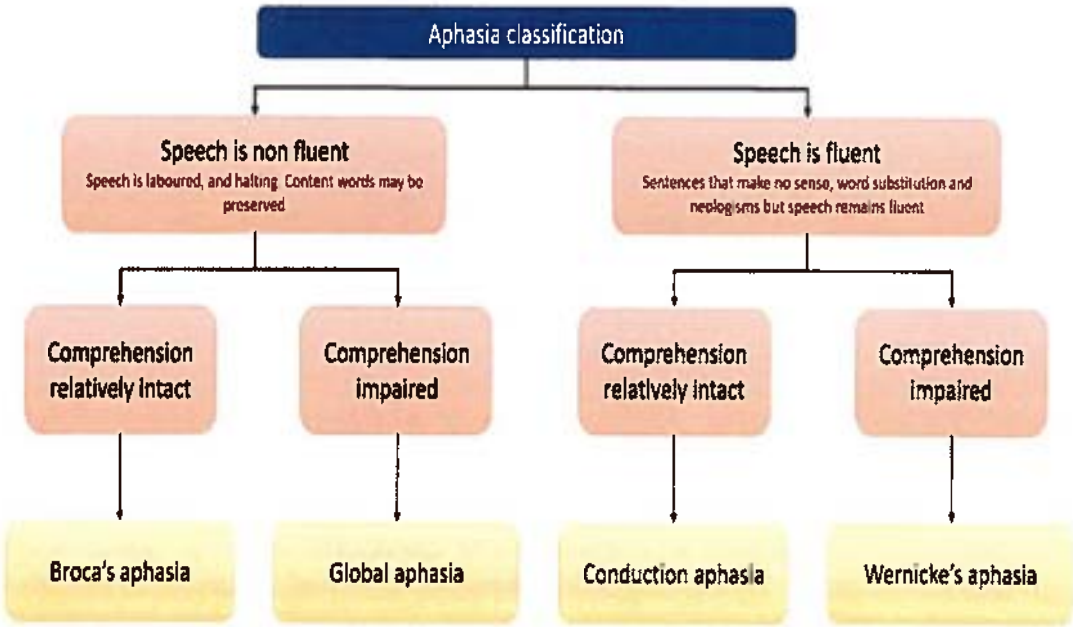
**N.B**: **Intra-cranial haemorrhage** can cause changes in the **ECG** which are typically **deep symmetrical T-wave inversion** and **prolonged QT interval**.

# Aphasia

The table below lists the major types of aphasia. Remember that dysarthria is different and refers to a motor speech disorder.

| Type of aphasia | Notes |
|---|---|
| Wernicke's (receptive) aphasia | Due to a lesion of the superior temporal gyrus. It is typically supplied by the inferior division of the left MCA<br>This area 'forms' the speech before 'sending it' to Broca's area. Lesions result in sentences that make no sense, word substitution and neologisms but speech remains fluent - 'word salad'<br>Comprehension is impaired |
| Broca's (expressive) aphasia | Due to a lesion of the inferior frontal gyrus. It is typically supplied by the superior division of the left MCA<br>Speech is non-fluent, laboured, and halting. Repetition is impaired<br>Comprehension is normal |
| Conduction aphasia | Classically due to a stroke affecting the arcuate fasiculus - the connection between Wernicke's and Broca's area<br>Speech is fluent but repetition is poor. Aware of the errors they are making<br>Comprehension is normal |
| Global aphasia | Large lesion affecting all 3 of the above areas resulting in severe expressive and receptive aphasia<br>May still be able to communicate using gestures |

Diagram showing the main types of aphasia




**More explanation:**

## Aphasia:

- In **Broca's** or **non-fluent** or **expressive** aphasia the patient is unable to name objects with poor comprehension and repetition. It localises to the Broca's area in the left posterior inferior **frontal** gyrus.

- In **Wernicke's** or **fluent** or **receptive** aphasia the patient is able to form correct grammatical sentences but language content is incorrect. It localises to the dominant superior **temporal** gyrus. There is poor comprehension and repetition but verbal output is fluent.

- **Transcortical motor aphasia** which localises to the anterior superior frontal lobe, the patient is able to repeat and have good comprehension and repetition but is unable to express themselves and have halting, effortful speech with intact repetition, Patients also have impaired writing skills.

- **Transcortical sensory aphasia** has impaired auditory comprehension with intact repetition and fluent speech, but the patient is unable to follow verbal commands with fluent grammatical speech. It differs from Wernicke's aphasia in that patients still have intact repetition, and exhibit cholalia (the compulsive repetition of words).

- **Conduction aphasia.** It is characterised by frequent speech errors, impaired repetition, and reduced phonological short-term memory and naming difficulties. In contrast to other forms of dysphasia, speech output is otherwise fluent and grammatically correct. Comprehension is intact.

- **Anomic aphasia** (also known as **nominal aphasia**) results in word finding difficulties. On closer examination there may also be repetition problems and comprehension problems but these are typically mild compared to other aphasia syndromes.

- **Global** aphasia results in **an almost mute patient**: there is poor verbal output, comprehension, repetition and understanding. With deficits in **all** aspects of language: spontaneous speech, naming, repetition, auditory comprehension, reading and writing. It is commonly seen in patients with large infarctions of the left cerebral hemisphere, usually due to occlusion of the internal carotid or middle cerebral artery. The visual centres remain intact and therefore patients are able to follow instructions shown to them.

- **Aphemia** is a type of aphasia in which there is severe dysarthria and impairment of verbal output. There is intact comprehension. It is believed to be the result of pars opercularis, inferior pre-Rolandic gyrus or subcortical lesions.

## Spinal cord lesions

### Motor lesions

**Amyotrophic lateral sclerosis** (motor neuron disease)

- affects both upper (corticospinal tracts) and lower motor neurons
- results in a combination of upper and lower motor neuron signs

**Poliomyelitis**

- affects anterior horns resulting in lower motor neuron signs

## Combined motor and sensory lesions

| Disorder | Tracts affected | Clinical notes |
|---|---|---|
| Brown-Sequard syndrome (spinal cord hemisection) | 1) Lateral corticospinal tract<br>2) Dorsal columns<br>3) Lateral spinothalamic tract | 1) **Ipsilateral spastic paresis** below lesion<br>2) Ipsilateral loss of proprioception and vibration sensation<br>3) **Contralateral loss of pain and temperature sensation** |
| Subacute combined degeneration of the spinal cord (vitamin B12 & E deficiency) | 1) Lateral corticospinal tracts<br>2) Dorsal columns<br>3) Spinocerebellar tracts | 1) Bilateral spastic paresis<br>2) Bilateral loss of proprioception and vibration sensation<br>3) Bilateral limb ataxia |
| **Friedrich's ataxia** | Same as **subacute combined degeneration of the spinal cord** (see above) | Same as subacute combined degeneration of the spinal cord (see above)<br>In addition cerebellar ataxia → other features e.g. intention tremor |
| **Anterior spinal artery occlusion** | 1) Lateral corticospinal tracts<br>2) Lateral spinothalamic tracts | 1) Bilateral spastic paresis<br>2) Bilateral loss of pain and temperature sensation |
| **Syringomyelia** | 1) Ventral horns<br>2) Lateral spinothalamic tract | 1) Flacid paresis (typically affecting the intrinsic hand muscles)<br>2) Loss of pain and temperature sensation |
| Multiple sclerosis | Asymmetrical, varying spinal tracts involved | Combination of motor, sensory and ataxia symptoms |

## Sensory lesions

| Disorder | Tracts affected | Clinical notes |
|---|---|---|
| Neurosyphilis (tabes dorsalis) | Dorsal columns | Loss of proprioception and vibration sensation |

## Brown-Sequard syndrome

It is a loss of sensation and motor function that is caused by the **lateral hemisection of the spinal cord.**

**Ipsilateral** signs include **pyramidal** weakness and **dorsal column** dysfunction (joint position and light touch) and **contralateral** signs include **spinothalamic** dysfunction (pinprick and temperature).

### Features:

- Ipsilateral loss of fine touch, vibration and proprioception.
- Ipsilateral hyperreflexia and extensor planter reflex.
- **Contralateral** loss of **pain and temperature** sensation.
- Segmental anaesthesia at the level of the lesion.

Complete syndrome picture is rare and many patient may only exhibit some features.

### Causes:

- Trauma is the common cause.
- Demyelination due to multiple sclerosis.
- Any lateral cord lesion (Ischaemia, haemorrhage, granuloma, tumour etc.

## Spastic paraparesis

Spastic paraparesis describes an **UMN** upper motor neuron pattern of weakness in the lower limbs. (i.e. weakness in both lower limbs, increased tone in both legs and brisk reflexes with normal upper limbs).

### Causes:

- **Cord compression**: trauma, tumour
- **Parasagittal meningioma**
- Demyelination e.g., **multiple sclerosis**
- **Transverse myelitis** e.g., **HIV**
- **Syringomyelia**
- **Hereditary spastic paraplegia**
- Tropical spastic paraparesis
- Osteoarthritis of the cervical spine

# Syringomyelia

## Overview:

- Development of cavity (**syrinx**) within the spinal cord that produce progressive myelopathy.
- Symptoms begins insidiously in adolescence or early adulthood, progress irregularly, and may undergo spontaneous arrest for several years; most patients acquire a cervical-thoracic scoliosis.
- If extends into **medulla** then termed **syringobulbia.**

## Causes:

- Strongly associated (> 50%) with the **Arnold-Chiari malformation.**
- trauma
- tumors
- idiopathic

## Features:

- May be **asymmetrical initially**.
- **Slowly progressives**, possibly over years.
- Motor: **wasting** and **weakness** of arms.
- Sensory: **Spinothalamic** sensory loss (**pain** and **temperature**).
- **Loss of reflexes**, bilateral upgoing planters.
- Horner's syndrome due to compression of the sympathetic chain, but this is rare
  - bowel and bladder dysfunction
- scoliosis will occur over a matter of years if the syrinx is not treated

## Investigations

- **MRI** is the investigation of choice
- **Myelography** used to confirm the diagnosis but was associated with more deterioration.

## Treatment

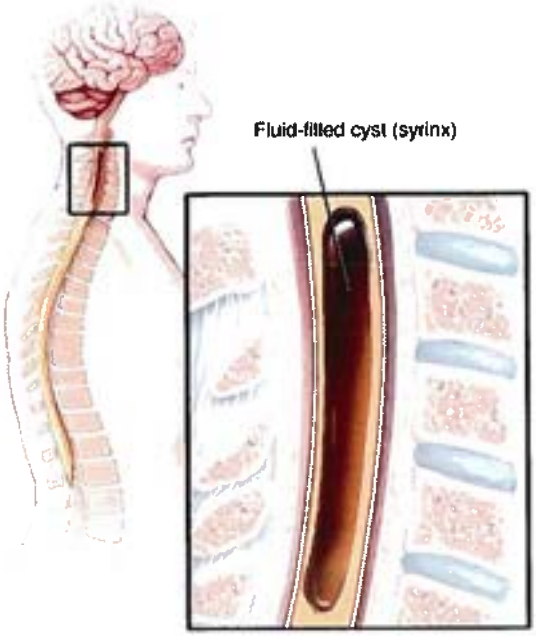
will be directed at treating the cause of the syrinx. In patients with a persistent or symptomatic syrinx, a shunt into the syrinx can be placed.

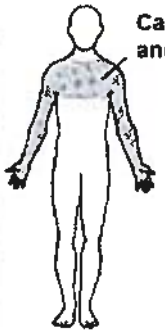
**Syringomyelia** >> **Spinothalamic** sensory loss (**pain** and **temperature**).

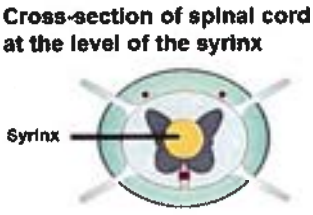
## Localization of the lesion:

- At syrinx (there is anterior horn cell involvement) → LMNL weakness.
- At central decussating fibers (spinothalamic tract) → dissociated sensory loss with late development of neuropathic arthropathy.
- At corticospinal tracts below the level of the syrinx → spastic paraplegia.

**EX**: A 35-year-old woman presents with **pains in the right arm**. She has **wasting** and **weakness** of the intrinsic muscles of the right hand, **absent tendon reflexes** in the right arm and **impaired pinprick sensation** in the right hand and forearm.
The most likely diagnosis >>> **Syringomyelia**




A fluid filled cavity within the cord develops, typically between C2 to T9, compressing the cord from inside to out.

The presence of loss of pain and temperature sensation in a 'cape like' distribution is highly suggestive of syringomyelia.

# Transverse myelitis (TM)

- It is an **inflammatory lesion** that can affects the cord.
- Constitutional symptoms such as headache and fever are common as is pain.
- Signs are indistinguishable from those caused by cord compression and again **all sensory aspects are equally affected** with no sparing of proprioception.
- The clinical signs are caused by an **interruption in ascending and descending pathways in the transverse plane of the spinal cord**.
- **A sensory level is characteristic**.
- **Midline or dermatomal neuropathic pain** can be present.
- **Urinary** incontinence or retention,
- **bowel** incontinence or constipation,
- and **sexual** dysfunction are common but vary in severity.

These signs develop over hours to days, and are usually **bilateral**.

## Causes:

- viral infections: varicella-zoster, herpes simplex, cytomegalovirus, Epstein-Barr, influenza, echovirus, human immunodeficiency virus
- bacterial infections: syphilis, Lyme disease
- post-infectious (immune mediated)
- first symptom of multiple sclerosis (MS) or neuromyelitis optica (NMO)

## Investigations:

- **MRI** is indicated to rule out the presence of **structural** lesions, and determine the presence of **myelitis** which **enhances with gadolinium** in the acute phase. There may be more than one area of myelitis, and the lesions usually span at least two vertebral segments. **In the acute phase the MRI may be normal**.
- **CSF analysis pleocytosis and / or elevated IgG index**

## Treatment

- in the acute phase aims to halt the progression and initiate resolution of the inflammatory cord lesion.
- **High doses Corticosteroids IV** are first line.
- **Plasma exchange** can be given to those who fail to respond.
- Patients with demyelinating disease can be started on long term immunosuppression.

**The prognosis** is highly **variable**, and improvement can take 3 months and longer to develop.

- **50% to 70%** of patients **have partial or complete recovery** ☺
- A rapidly progressive course, severe weakness, hypotonia and areflexia are predictors of poor prognosis.

## Subacute Combined Degeneration of spinal cord

**It is also known as Lichtheim's disease.**

It refers to **degeneration** of the **posterior** and **lateral** columns of the spinal cord as a result of **Vit B12 deficiency** (most common), **Vit E deficiency** or **Friedrich's ataxia.**

It is usually associated with pernicious anaemia.

### Features:

- Patchy losses of myelin in the dorsal and lateral columns.
- Present with progressive weakness of legs, arms, trunk, tingling and numbness.
- **Visual** and **mental** changes may also be present.
- **Bilateral spastic paresis** with diminished **pressure**, **vibration** and **touch** sense.
- **Positive Babinski** sign may be seen.
- **Extensor plantars with absent ankle reflexes**

Prolonged deficiency of Vit B12 **(>3 months)** leads to **irreversible** nervous system damage.

**If someone is deficient on Vit B12 and folic acid, the Vit B12 deficiency should be treated first to avoid precipitating SCD of the cord.**

### Diagnosis

- **MRI** typically shows **increased signal on T2~weighted imaging** in the dorsal columns

### Treatment:

with Vit B12 results in partial to full recovery, depending on the duration and extent of neurodegeneration.

# CRANIAL NERVES

## Visual field defects

**Visual field defect is a manifestation of the following pathology:**
- **Occipital** lobe (**homonymous** hemianopia)
- **Temporal** lobe (**superior quadrantanopia**) or
- **Parietal** lobe (**inferior quadrantanopia**).

### The main points for the exam are:

- **Right homonymous hemianopia** means visual field defect to the right, i.e. Lesion of **left optic tract.**
- **Incongruous** defects = optic tract lesion
- **Congruous** defects = optic radiation lesion or occipital cortex

A congruous defect (defect is approximately the same in each eye) simply means complete or symmetrical visual field loss and conversely an incongruous defect is incomplete or asymmetric.

### Homonymous hemianopia:

- **Incongruous** defects: lesion of **optic tract.**
- **Congruous** defects: lesion of **optic radiation** or **occipital cortex.**
- **Macula sparing**: lesion of occipital cortex.

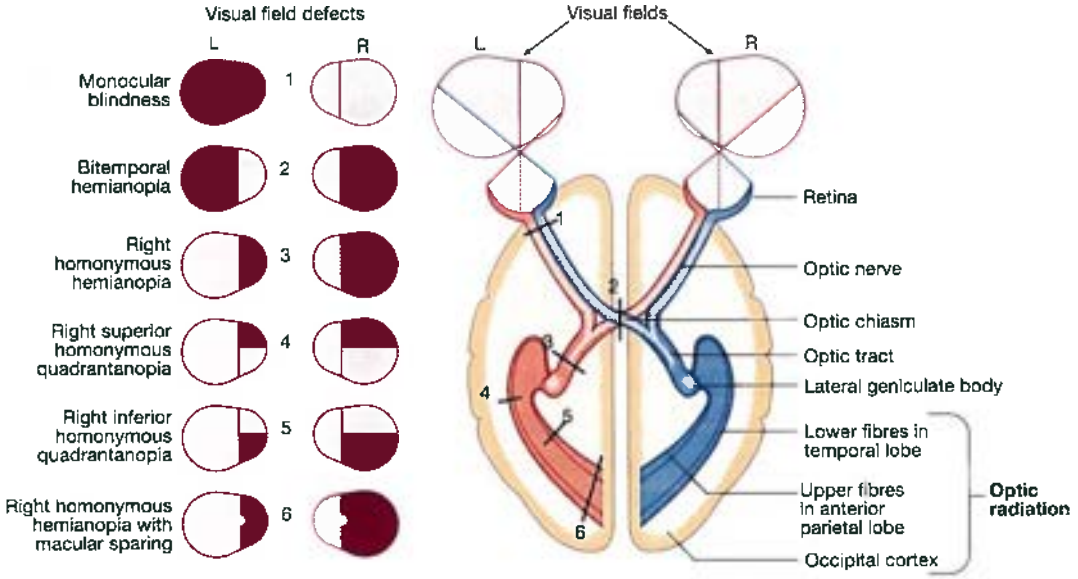
**EX:** Left congruous homonymous hemianopia >> lesion in Right occipital cortex.

### Homonymous quadrantanopias:

- **PITS** (**P**arietal-**I**nferior, **T**emporal-**S**uperior).
- **S**uperior: lesion of **t**emporal lobe.
- **I**nferior: lesion of **p**arietal lobe.

### Bitemporal hemianopia:

- Lesion of **optic chiasm.**
- **Upper** quadrant defect > lower quadrant defect = **inferior** chiasmal compression, commonly a **Pituitary tumour.**
- **Lower** quadrant defect > upper quadrant defect = **superior** chiasmal compression, commonly a **Craniopharyngiomas.**




Visual pathways and visual field defects. Schematic representation of eyes and brain in transverse section.

## Nystagmus

It is defined as involuntary oscillations of the eyes.

This may be **pendular** when the oscillations are equal in rate and amplitude, or **jerking** when there are quick and slow phases (the quicker phase is used to define the direction).

### Causes:

- Visual disturbances.
- Labyrinth lesions.
- The central vestibular connections.
- Brain stem lesion.
- Cerebellar lesion.

## Types:

- Nystagmus which changes with the direction of the gaze: involvement of vestibular nuclei.
- Pendular: mostly due to loss of macular vision, but could be in diffuse brain stem lesions.
- Jerking regardless of the direction of gaze: labyrinthine or cerebellar lesion.
- Jerking on lateral gaze, and fast in the direction of gaze: brain stem or cerebellar lesion.
- Nystagmus confined to one eye: nerve or muscle lesion, or medial longitudinal bundle (MLB) lesion.
- Nystagmus restricted to the abducting eye on lateral gaze (ataxic nystagmus): lesion of the MLB between mid-brain and pons as in multiple sclerosis (MS).
- Nystagmus occurring on **upward** gaze with the fast component upwards (upbeat nystagmus) may be due to a lesion in the mid-brain at the level of the superior colliculus.
- **Downbeat nystagmus (fast phase downwards) suggests a lesion in the lower part of the medulla. It is therefore typical of the Arnold-Chiari malformation.**
- Wernicke's encephalopathy or thiamine deficiency is a rare cause of downbeat nystagmus.

| | |
|---|---|
| **Upbeat** nystagmus: | Cerebellar vermis lesions. |
| **Downbeat** nystagmus-foramen magnum lesions: | **Arnold-Chiari malformation.** |
| **MLB**-→coordinate lateral rectus of one side with medial rectus of the other side. | |

# Miosis (small pupil): causes

## Causes of miosis (small pupil)

- **Horner's syndrome**
- **Argyll-Robertson pupil**
- **Pontine haemorrhage**
- Congenital
- Senile miosis
- **Drugs:**
  - **Opiates**
  - **Organophosphate toxicity**
  - Parasympathomimetic: pilocarpine.

**Argyll-Robertson pupil**: small irregular pupils that do not react to light but react to accommodation.

Referred to as the **"Whore's Eye"** because of the association with **tertiary syphilis** and because of the convenient **mnemonic** that, like a **prostitute**, they **"can accommodate but do not react".**

**Another mnemonic** used for the Argyll-Robertson Pupil **(ARP)** is Accommodation Reflex Present **(ARP)** but Pupillary Reflex Absent **(PRA).**

Causes: Multiple sclerosis, sarcoidosis, DM.

## Horner's syndrome

**Horner's: triad of ptosis, miosis and anhydrosis**

**Horner's syndrome - Anhydrosis determines site of lesion:**

- Head, arm, trunk = central lesion: stroke, Syringomyelia.
- Just face = pre-ganglionic lesion: Pancoast's, cervical rib.
- Absent = post-ganglionic lesion: carotid artery.

### Features:

- **Ptosis.**
- **Miosis** (small pupil).
- **Anhidrosis** (loss of sweating one side).
- **Enophthalmos**: (sunken eye): (in reality the appearance is due to a narrow palpebral aperture rather than true Enophthalmos).
- Facial flushing due to vasodilation

Causes:**monomer (STC)**

| Central lesions | Pre-ganglionic lesions | Post-ganglionic lesions |
|---|---|---|
| Anhydrosis of the face, arm and trunk | Anhydrosis of the **face** | **No anhydrosis** |
| ▪ **S**troke<br>▪ **S**yringomyelia<br>▪ Multiple **s**clerosis<br>▪ Tumour<br>▪ Encephalitis | ▪ Pancoast's **t**umour<br>▪ **T**hyroidectomy<br>▪ **T**rauma<br>▪ Cervical rib | ▪ **C**arotid artery dissection<br>▪ **C**arotid aneurysm<br>▪ **C**avernous sinus thrombosis<br>▪ **C**luster headache |

### Distinguishing between causes:

- Heterochromia (difference in iris colour) is seen in congenital Horner's
- Anhidrosis: see before.

### Orbital apex syndrome

- **The combination of optic neuropathy, proptosis, chemosis, Horner syndrome ophthalmoplegia and involvement of the first branch of the trigeminal nerve is typical of orbital apex syndrome**
- The presence of proptosis with swelling of eyelids and chemosis (swelling of the ocular Surface membranes), indicates significant mass extension within the orbit
- The orbital apex syndrome (involvement of cranial nerves II, III, IV, and V1) is a superior orbital fissure syndrome with loss of vision

## Third nerve III palsy

### Features:

- **Eye is deviated 'down and out'.**
- **Ptosis.**
- **Mydriasis** (Pupil may be dilated) (sometimes called a 'surgical' third nerve palsy).
- **Pain only if** due to a posterior communicating artery aneurysm.

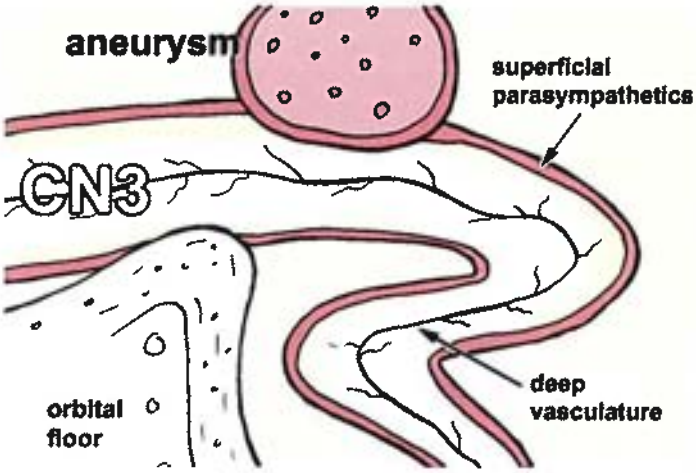
| |
|---|
| Ptosis + **Miosis** (Constricted pupil) >>> **Horner's** Syndrome<br>Ptosis + **Mydriasis** (Dilated pupil) >>> **3 rd. Nerve palsy** |

### Causes:

- DM
- Vasculitis e.g., temporal arteritis, SLE
- False localizing sign due to uncal herniation through tentorium if raised ICP
- **Posterior communicating artery aneurysm (PCAA)** (pupil dilated)
- **Cavernous sinus thrombosis**
- **Weber's syndrome**: Ipsilateral third nerve palsy with contralateral hemiplegia -caused by midbrain strokes (cerebral peduncle).
- Other possible causes: amyloid, multiple sclerosis

*This term is usually associated with sixth nerve palsies but it may be used for a variety of neurological presentations

**Painful third nerve palsy = posterior communicating artery aneurysm** (i.e. EX. **Third nerve palsy** with **headache** and meningism >>> should exclude posterior communicating artery aneurysm).




## Fourth nerve palsy

### Overview

- supplies superior oblique (depresses eye, moves inward)

### Features

- vertical diplopia
  - classically noticed when reading a book or going downstairs
- subjective tilting of objects (torsional diplopia)
- the patient may develop a head tilt, which they may or may not be aware of
- when looking straight ahead, the affected eye appears to deviate upwards and is rotated outwards

## Trigeminal neuralgia

Trigeminal neuralgia is a pain syndrome characterised by severe unilateral pain.

The vast majority of cases are idiopathic but compression of the trigeminal roots by tumours or vascular problems may occur.

## Features

**The International Headache Society** defines trigeminal neuralgia as:

- A unilateral disorder characterised by brief electric shock-like pains, abrupt in onset and termination, limited to one or more divisions of the trigeminal nerve.
- The pain is commonly evoked by light touch, including washing, shaving, smoking, talking, and brushing the teeth (trigger factors), and frequently occurs spontaneously.
- Small areas in the nasolabial fold or chin may be particularly susceptible to the precipitation of pain (trigger areas).
- The pains usually remit for variable periods.

**NICE Clinical Knowledge** Summaries list the following as red flag symptoms and signs suggesting a serious underlying cause:

- Sensory changes
- Deafness or other ear problems
- History of skin or oral lesions that could spread perineurally
- Pain only in the ophthalmic division of the trigeminal nerve (eye socket, forehead, and nose), or bilaterally
- Optic neuritis
- A family history of multiple sclerosis
- Age of onset before 40 years

## Management

- carbamazepine is first-line
- failure to respond to treatment or atypical features (e.g. < 50 years old) should prompt referral to neurology

# Acoustic neuroma

Acoustic neuromas (more correctly called **vestibular schwannomas**: it is a **benign** primary intracranial tumour of the **myelin forming cells** of the vestibulocochlear nerve CN **VIII**).

It accounts for approximately 5% of intracranial tumours and **90 % of cerebellopontine angle**.

The term "acoustic" is a misnomer as the tumour rarely arises from the acoustic (or cochlear) division of the vestibulocochlear nerve.

**Features** can be predicted by the affected cranial nerves:

- Cranial nerve (**5**) V: **absent corneal reflex**
- Cranial nerve (**7**) VII: facial palsy
- Cranial nerve (**8**) VIII: hearing loss, vertigo, tinnitus

Bilateral acoustic neuromas are seen in neurofibromatosis type 2.

### Investigation

MRI of the cerebellopontine angle is the investigation of choice.
Audiometry is also important as only 5% of patients will have a normal audiogram.

**Management** is with either surgery, radiotherapy or observation.

Loss of corneal reflex → think of Acoustic neuroma

## Vertigo

Vertigo may be defined as the false sensation that the body or environment is moving.

The table below lists the main characteristics of the most important causes of vertigo

| Disorder | Notes |
|---|---|
| **Viral labyrinthitis** | Recent viral infection<br>Sudden onset<br>Nausea and vomiting<br>Hearing may be affected |
| **Vestibular neuronitis** | Recent viral infection<br>Recurrent vertigo attacks lasting hours or days<br>No hearing loss |
| **Benign paroxysmal positional vertigo** | Gradual onset<br>Triggered by change in head position<br>Each episode lasts 10-20 seconds |
| **Meniere's disease** | Associated with hearing loss, tinnitus and sensation of fullness or pressure in one or both ears |
| **Vertebrobasilar ischaemia** | Elderly patient<br>Dizziness on extension of neck |
| **Acoustic neuroma** | Hearing loss, vertigo, tinnitus<br>Absent corneal reflex is important sign<br>Associated with neurofibromatosis type 2 |

### Other causes of vertigo include

- **posterior circulation stroke**
- trauma
- multiple sclerosis
- ototoxicity e.g. gentamicin

## Benign paroxysmal positional vertigo (BPPV)

It is one of the most common causes of vertigo encountered.

It is characterised by the sudden onset of dizziness and vertigo triggered by **changes in head position**.

The average age of onset is 55 years and it is less common in younger patients.

### Features:

- Vertigo triggered by change in head position (e.g. rolling over in bed or gazing upwards).
- May be associated with nausea.
- Each episode typically lasts 10-20 seconds.
- **Positive Dix-Hallpike manoeuvre.**
  - patient experiences vertigo
  - rotatory nystagmus

### Management

Symptomatic relief may be gained by:

- **Epley manoeuvre** (successful in around 80% of cases)
- Medication is often prescribed e.g. Betahistine (Betaserc ®) but it tends to be of limited value.
- Teaching the patient exercises they can do themselves at home, for example Brandt-Daroff exercises.

### Prognosis

- BPPV has a good prognosis and usually resolves spontaneously after a few weeks to months.

**MRCPUK part 1 exam:** H/O vertigo and dizziness precipitated by a change in head position. What is the most appropriate next step to confirm the diagnosis? **>> Dix-Hallpike manoeuvre**

# Meniere's disease

It is a disorder of the **inner ear** of **unknown** cause.

It is characterised by excessive pressure and progressive dilation of the endolymphatic system.

It is more common in **middle-aged adults** but may be seen at any age.

Meniere's disease has a **similar** prevalence in **both men and women**.

## Features:

- **Recurrent** episodes of **vertigo**, tinnitus and **hearing loss** (**sensorineural**, i.e. **+ve Weber's test**).
- Vertigo is usually the prominent symptom.
- A sensation of **aural fullness** or **pressure** is now recognised as being common.
- Other features include **nystagmus** and a positive Romberg test
- Episodes last minutes to hours.
- Typically symptoms are unilateral but bilateral symptoms may develop after a number of years.

## Natural history:

- Symptoms **resolve** in the **majority** of patients **after 5-10 years**
- Some patients may be left with hearing loss.
- Psychological distress is common.

## Management:

- ENT assessment is required to confirm the diagnosis.
- Patients should inform the DVLA. The current advice is to cease driving until satisfactory control of symptoms is achieved.
- Acute attacks:
  - Buccal or intramuscular **Prochlorperazine**.
  - Admission is sometimes required.
- **Prevention**: **Betahistine** may be of benefit.

# Vestibular neuronitis

Vestibular neuronitis is a cause of vertigo that often develops following a viral infection.

## Features

- recurrent vertigo attacks lasting hours or days
- nausea and vomiting may be present
- **horizontal nystagmus is usually present**
- no hearing loss or tinnitus

## Differential diagnosis

- viral labyrinthitis
- posterior circulation stroke: the HiNTs exam can be used to distinguish vestibular neuronitis from posterior circulation stroke

## Management

- buccal or intramuscular prochlorperazine is often used to provide rapid relief for severe cases
- a short oral course of prochlorperazine, or an antihistamine (cinnarizine, cyclizine, or promethazine) may be used to alleviate less severe cases
- vestibular rehabilitation exercises are the preferred treatment for patients who experience chronic symptoms

# Tinnitus (causes)

Tinnitus is the perception of sounds in the ears or head that do not come from an outside source. Around 1 in 10 people will experience an episode of tinnitus at some point in their life.
Although sometimes considered a 'minor' symptom of 'ringing in the ears' it can be distressing to patients and may occasionally be a sign of a serious underlying condition.

## Causes of tinnitus include:

| Idiopathic | An underlying cause will not be found in the majority of patients. | |
|---|---|---|
| **Meniere's disease** | Associated with hearing loss, vertigo, tinnitus and sensation of fullness or pressure in one or both ears | |
| **Otosclerosis** | • Onset is usually at 20-40 years<br>• Conductive deafness<br>• Tinnitus<br>• Normal tympanic membrane although 10% of patients may have a 'flamingo tinge', caused by hyperaemia<br>• Positive family history | |
| **Sudden onset sensorineural hearing loss (SSNHL)** | Around 80% of **Acoustic neuroma** | Hearing loss, vertigo, tinnitus<br>Absent corneal reflex is important sign<br>Associated with neurofibromatosis type 2 |
| **Hearing loss** | Causes include excessive loud noise and presbycusis | |
| **Drugs** | • Aspirin/NSAIDs<br>• Aminoglycosides<br>• Loop diuretics<br>• Quinine | |
| **Impacted ear wax** | Usually obvious on otoscopy | |

### Assessment

- audiological assessment
  - detect underlying hearing loss
- imaging
  - not all patients will require imaging. Generally, non-pulsatile tinnitus does not require imaging unless it is unilateral or there are other neurological or ontological signs. MRI of the internal auditory meatuses (IAM) is first-line
  - pulsatile tinnitus generally requires imaging as there may be an underlying vascular cause. Magnetic resonance angiography (MRA) is often used to investigate pulsatile tinnitus

### Management

- investigate and treat any underlying cause
- amplification devices
  - more beneficial if associated hearing loss
- psychological therapy may help a limited group of patients
  - examples include cognitive behavioural therapy
- tinnitus support groups

## Rinne's and Weber's test

Performing both to allows differentiation of conductive and sensorineural deafness.

### Rinne's test:

- Tuning fork is placed over the mastoid process until the sound is no longer heard, followed by repositioning just over external acoustic meatus.
- Air conduction (AC) is normally better than bone conduction (BC).
- If BC > AC then conductive deafness.

### Weber's test:

- Tuning fork is placed in the middle of the forehead equidistant from the patient's ears.
- The patient is then asked which side is loudest.
- In unilateral **sensorineural** deafness, **sound** is **localised** to the **unaffected** side.
- In unilateral **conductive** deafness, sound is **localised** to the **affected** side.

## Interpretation of Rinne and Weber tests

| | Rinne result | Weber result |
|---|---|---|
| **Normal** | Air conduction > bone conduction bilaterally | Midline |
| **Conductive hearing loss** | Bone conduction > air conduction in affected ear<br>Air conduction > bone conduction in unaffected ear | Lateralises to affected ear |
| **Sensorineural hearing loss** | Air conduction > bone conduction bilaterally | Lateralises to unaffected ear |

**EX**: Weber's test: If sound is localized to the **Rt**. side: so either **Rt**. **conductive** deafness or **Lt sensorineural** deafness

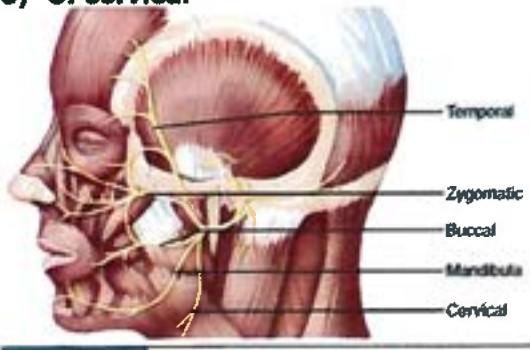
## Facial nerve

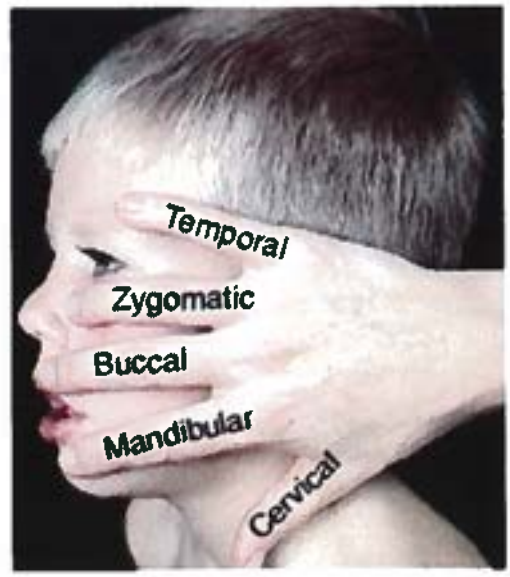
**Supply:** 'face, ear, taste, and tear':

1) **Face**: muscles of facial expression.
2) **Ear**: nerve to stapedius muscle >> paralysis >> Hyperacusis.
3) **Taste**: supplies anterior two-thirds of tongue.
4) **Tear**: parasympathetic fibres to lacrimal glands, also salivary glands >> Overflow of tears may occur but hyperlacrimation does not.

**Facial nerve branches (mnemonic)** (superior to inferior) **as** they exit the anterior border of the parotid gland: **T**o **Z**anzibar **B**y **M**otor **C**ar

1) **T: temporal**
2) **Z: zygomatic**
3) **B: buccal**
4) **M: mandibular**
5) **C: cervical**



## Causes of unilateral facial nerve palsy:

| UMNL | LMNL |
|---|---|
| **Stroke** | - Bell's palsy.<br>- Ramsay-Hunt syndrome (due to HZV).<br>- Acoustic neuroma.<br>- Parotid tumours.<br>- Multiple sclerosis (may also cause an UMN palsy).<br>- HIV.<br>- DM. |

## Causes of bilateral facial nerve palsy:

- **Sarcoidosis**
- GBS.
- MG.
- Polio.
- **Lyme** disease.
- Bilateral Bell's palsy.

## LMN vs. UMN:

- **Upper** motor neuron lesion **'spares' upper** face i.e. forehead
- **Lower** motor neuron lesion affects **all** facial muscles

Facial palsy + convergent squint→ lesion is in **pons** as VI th is encircled by VII.

# Bell's palsy

Bell's palsy may be defined as an acute, unilateral, idiopathic, facial nerve paralysis.
The aetiology is unknown although the role of the HSV has been investigated previously.

## Features:

- **Lower motor neuron facial nerve palsy** i.e., forehead affected.
- Patients may also notice **post-auricular pain** (may precede paralysis), altered taste, dry eyes, **hyperacusis (present in 30% of cases)**.
- You need to be confident that there are no features of Guillain-Barré (test reflexes), or brain stem vascular disease or space occupying lesion.

## Management:

- In the past a variety of treatment options have been proposed including no treatment, prednisolone only and a combination of acyclovir and prednisolone.

- Following a National Institute for Health randomised controlled trial it is now recommended that **prednisolone 25mg bid for 10 days** should be prescribed for patients **within 72 hours of onset** of Bell's palsy. Adding in acyclovir gives no additional benefit.
- **UpToDate recommends the addition of antivirals for severe facial palsy**
- **Eye care** is important - prescription of artificial tears and eye lubricants should be considered.
- **If they are unable to close the eye at bedtime, they should tape it closed using microporous tape.**

### Follow-up:

- if the paralysis shows no sign of improvement after 3 weeks, refer urgently to ENT
- a referral to plastic surgery may be appropriate for patients with more long-standing weakness e.g. several months

### Prognosis:

- most people with Bell's palsy make a full recovery within 3-4 months
- if untreated around 15% of patients have permanent moderate to severe weakness.

**N.B:** **Upper** motor neuron lesion of facial nerve **'spares' upper** face

**N.B:** A vesicular rash around the ear would suggest a diagnosis of Ramsey Hunt syndrome

## Ramsay Hunt syndrome

Ramsay Hunt syndrome (herpes zoster oticus) is caused by the reactivation of the varicella zoster virus in the geniculate ganglion of the seventh cranial nerve.

### Features

- auricular pain is often the first feature
- facial nerve palsy
- **vesicular rash around the ear**
- other features include vertigo and tinnitus

### Management

- **oral aciclovir and corticosteroids** are usually given

# bulbar and pseudobulbar palsy

**Comparison of bulbar and pseudobulbar palsy**

| Pseudobulbar Palsy | Bulbar Palsy |
|---|---|
| Bilateral damage or injury of corticobulbar tracts to nerve nuclei of cranial nerves V, VII, IX, X XI, and XII<br>• Upper motor neuron palsy of the respective muscles | Bilateral damage or injury of the nerve nuclei of cranial nerves IX, X, XI, and XII<br>• Lower motor neuron palsy of the respective muscles |
| **lower motor neurone signs absent** | **lower motor neurone signs present** |
| Spastic tongue (no wasting / fasciculations) | Wasted tongue, fasciculations |
| **Spastic dysarthria** | Nasal speech |
| **Labile emotions** | Normal emotions |
| **Facial expressions: absent** | Facial expression: normal |
| **Gag reflex: brisk (exaggerated)** | Gag reflex: absent |
| **Jaw jerk: exaggerated** | Jaw jerk: normal |

# Parkinson's disease

## Parkinson's disease: please refer to Nice guidelines 2017

It is a progressive neurodegenerative condition caused by **degeneration** of **dopaminergic** neurons in the **substantia nigra (SN)**.

**Mutations** in either the **parkin gene** or **UCHL1** lead to **impaired protein degradation**.

This results in a classic **triad** of features: **bradykinesia**, **tremor** and **rigidity**.

The symptoms of Parkinson's disease are characteristically **asymmetrical**.

**Asymmetrical** symptoms (tremors) point towards a diagnosis of **idiopathic Parkinson's disease** rather than **Parkinsonism of another cause e.g. Drug-induced Parkinsonism.**

## Epidemiology:

- Around twice as common in **men**
- Mean age of diagnosis is **65** years

### 1) Bradykinesia:

- Poverty of movement also seen, sometimes referred to as **hypokinesia**.
- **Short, shuffling steps** with **reduced arm swinging**
- Difficulty in initiating movement

### 2) Tremor:

- Typically, **'pill-rolling'**, i.e. in the thumb and index finger
- Most marked at **rest**, with **low** frequency **3-5 Hz**
- **Worse** when stressed or tired and with levodopa

### 3) Rigidity:

- **Lead pipe**
- **Cogwheel**: due to superimposed tremor

## Other characteristic features:

- **Mask-like facies**
- Flexed posture
- **Micrographia**
- Drooling of saliva
- Psychiatric features: **depression is the most common feature (affects about 40%);** dementia, psychosis and sleep disturbances may also occur.
- Impaired olfaction.
- REM sleep behaviour disorder.
- fatigue
- autonomic dysfunction:
  - postural hypotension

**NB**: **Diplopia** is not common in Parkinson's disease and may suggest an alternative cause of Parkinsonism such as **progressive supranuclear palsy**.

**NB**: Difficulty in initiating movement (bradykinesia), postural instability and unilateral symptoms (initially) >>> are typical of Parkinson's.

## Causes of Parkinsonism:

- Parkinson's disease
- Drug-induced e.g. antipsychotics, metoclopramide - see below
- **Progressive supranuclear palsy**
- **Multiple system atrophy**
- **Wilson's disease**
- Post-encephalitis

- Dementia pugilistica (secondary to chronic head trauma e.g. boxing)
- Toxins: carbon monoxide, Carbon disulphide, MPTP (methyl-phenyl tetrahydropyridine), Manganese and cycad nut

### Drug-induced Parkinsonism:

- Phenothiazines: e.g. **chlorpromazine, prochlorperazine**
- Butyrophenones: **haloperidol**, droperidol
- **Metoclopramide**

It has slightly different features to Parkinson's disease:

- **Motor** symptoms are generally **rapid onset** and **bilateral.**
- Rigidity and rest tremor are uncommon.

**N.B:** Domperidone does not cross the blood-brain barrier and therefore does not cause extra-pyramidal side-effects.

**NB**: **Anticholinergic** treatment (for example, benzhexol) is the treatment of choice for **tremor** predominantly Parkinson's disease.
**L-dopa** and **dopamine agonists** are the treatment of choice for **bradykinesia** and **rigidity**.

## Parkinson's disease (PD): management

Currently accepted practice in the management of patients with Parkinson's disease (PD) is **to delay treatment until the onset of disabling symptoms** and **then to introduce a dopamine receptor agonist.**

### Summary of first-line treatment:

- if the motor symptoms are affecting the patient's quality of life: levodopa
- if the motor symptoms are not affecting the patient's quality of life: dopamine agonist (non-ergot derived), levodopa or monoamine oxidase B (MAO-B) inhibitor

### 1) Dopamine receptor agonists:

- Favoured for Pt.>75 Yrs. old.
- e.g., **Bromocriptine, Cabergoline, Apomorphine, Ropinirole**.
- **Ergot**-derived dopamine receptor agonists (Bromocriptine, Cabergoline, and **Pergolide**) have been associated with **pulmonary, cardiac and retroperitoneal fibrosis**.

**Ropinirole** is the **least** associated with tissue fibrosis.
**Ropinirole is** a **non**-ergot derived dopamine agonist licensed for ttt of Parkinsonism & restless leg syndrome.
It is a reasonable choice for **first line therapy** in **younger** patients.

- The Committee on Safety of Medicines advice that an echocardiogram, ESR, creatinine and chest x-ray should be obtained prior to treatment and patients should be closely monitored.
- Patients should be warned about the potential for dopamine receptor agonists to cause **impulse control disorders** and **excessive daytime somnolence.**
- More likely than levodopa to cause **hallucinations** in older patients. **Nasal congestion** and **postural hypotension** are also seen in some patients.
- Dopamine agonists are thought to be associated with **less** on/off phenomena than L-Dopa based therapy and are seen as a reasonable choice for **first line therapy in younger patients**.

**Pergolide** was withdrawn from the US market in March 2007 due to concern regarding increased incidence of **valvular dysfunction**

## 2) Levodopa:

- **Favoured for Pt. < 75 Yrs. old.**
- If the patient is elderly, levodopa is sometimes used as an initial treatment.
- Usually combined with a **decarboxylase inhibitor** (e.g. Carbidopa or benserazide) to prevent peripheral metabolism of levodopa to dopamine.
- Dopa-decarboxylase inhibitors **reduce the extracerebral complications** of L-dopa therapy. These include nausea, vomiting, postural hypotension and cardiac arrhythmias.
- Reduced effectiveness with time (usually by 2 years).
- Unwanted effects:
  1) **Dyskinesia** (involuntary writhing movements).
  2) **'On-off' effect**.
  3) **Psychosis**, drowsiness.
  4) **Postural hypotension**
  5) **Cardiac arrhythmias**
  6) Dry mouth, anorexia, nausea and vomiting.
  7) Reddish discolouration of urine upon standing.

- Not use in neuroleptic induced Parkinsonism.

**Levodopa–carbidopa intestinal gel**

- Levodopa–carbidopa intestinal gel is currently available through an NHS
- England clinical commissioning policy. It is recommended that this policy is reviewed in light of this guidance

## 3) MAO-B (Monoamine Oxidase-B) inhibitors:

- e.g., Selegiline.
- Inhibits the breakdown of dopamine secreted by the dopaminergic neurons.

## 4) Amantadine:

- Mechanism is not fully understood, probably increases dopamine release and inhibits its uptake at dopaminergic synapses.
- SE: include ataxia, slurred speech, confusion, dizziness and livedo reticularis.

## 5) COMT (Catechol-O-Methyl Transferase) inhibitors:

- e.g., Entacapone, tolcapone.
- COMT is an enzyme involved in the breakdown of dopamine, and hence may be used as an adjunct to levodopa therapy.
- Used in conjunction with levodopa in patients with established PD.

## 6) Antimuscarinics:

- Block cholinergic receptors.
- Now used more to treat **drug-induced Parkinsonism** (i.e. Parkinsonism secondary to antipsychotic medications used in treatment of schizophrenia) rather than idiopathic Parkinson's disease.
- Also used in treatment of extrapyramidal symptoms (EPS) (Acute dystonic-dyskinetic reactions) of metoclopramide antiemetic.
- Help **tremor** and rigidity
- E.g. **Benztropine, Procyclidine, Trihexyphenidyl (Benzhexol).**

Potential benefits and harms of dopamine agonists, levodopa and MAO-B inhibitors

| | Levodopa | Dopamine agonists | Monoamine oxidase-B (MAO-B) inhibitors |
|---|---|---|---|
| Motor symptoms | More improvement in motor symptoms | Less improvement in motor symptoms | Less improvement in motor symptoms |
| Activities of daily living | More improvement in activities of daily living | Less improvement in activities of daily living | Less improvement in activities of daily living |
| Motor complications | More motor complications | Fewer motor complications | Fewer motor complications |
| Adverse events (Excessive sleepiness, hallucinations and impulse control disorders; see the summary of product characteristics for full information on individual medicines) | Fewer specified adverse events | More specified adverse events | Fewer specified adverse events |

**Potential benefits and harms of dopamine agonists, MAO-B inhibitors, COMT inhibitors and amantadine**

| | Dopamine agonists | Monoamine oxidase-B (MAO-B) inhibitors | Catechol-O-methyl transferase (COMT) inhib. | Amantadine |
|---|---|---|---|---|
| Motor symptoms | Improvement in motor symptoms | Improvement in motor symptoms | Improvement in motor symptoms | No evidence of improvement in motor symptoms |
| Activities of daily living | Improvement in activities of daily living | Improvement in activities of daily living | Improvement in activities of daily living | No evidence of improvement in activities |
| Off time | More off-time reduction | Off-time reduction | Off-time reduction | No studies reporting this outcome |
| Adverse events | Intermediate risk of adverse events | Fewer adverse events | More adverse events | No studies reporting this outcome |
| Hallucinations | More risk of hallucinations | Lower risk of hallucinations | Lower risk of hallucinations | No studies reporting this outcome |

## Progressive Supranuclear Palsy (PSP)

### Overview:

- It is also known as **Steele-Richardson-Olszewski Syndrome (SROS)**
- A **'Parkinson Plus' syndrome**
- It is degenerative disease with gradual deterioration and death of selected areas of the brain. About 6 people per 100,000.

### Features: (Triad):

- **Parkinsonism**
  - bradykinesia is prominent
- **Impairment of vertical gaze** due to supranuclear paralysis of upward and **downward gaze** (the down gaze worse than up gaze - patients may complain of difficultly reading or descending stairs)
- **Cognitive impairment**
  - primarily frontal lobe dysfunction

- **postural instability and falls**
  - patients tend to have a stiff, broad-based gait
- dementia

### Management:

- **Poor response to L-dopa**

### Prognosis

- usually fatal within 5-10 years.

**PSP (Triad)**: Parkinsonism+ impairment vertical gaze + Cognitive impairment

## Essential tremor

Essential tremor (previously called benign essential tremor) is an **AD autosomal dominant** condition which usually affects both upper limbs.

### Features:

- **Postural tremor**: **worse if arms outstretched** (usually 6-8 Hz).
- It is **worse** on **movement** and during **stress.**
- **Improved by alcohol and rest**
- Most common cause of **titubation (head tremor)**

### Management:

- **Propranolol** is first-line
- **Primidone** (anticonvulsant) is sometimes used (as in case which cannot give propranolol like in bronchial asthma).

**NB**: **Anxiety** and **drugs** (for example, **salbutamol**, **sodium valproate**, **theophylline**, **and amiodarone**) are commonly associated with limbs tremor.

**MRCPUK part 1 exam:** H/O involuntary movements of the head, worse on movement and during stress and relieved by alcohol and sleep. What is the most likely diagnosis? >> **Essential tremor** (Essential tremor is the most common cause of titubation (head tremor)

**MRCPUK part 1 exam**: H/O tremor of the arms, which is worse when arms are outstretched. His father suffered from a similar complaint. What is the most suitable first-line treatment? >> **Propranolol**

# Holmes tremor

**Holmes's tremor >> lesion in the red nucleus**

## Overview

- Holmes tremor or rubral tremor is caused by a lesion in the red nucleus.

## Causes

- Previous stroke of the red nucleus (the most common cause), head trauma, and demyelinating diseases.

## Pathophysiology

- It is assumed that a double lesion is required to develop HT, including the dopaminergic nigrostriatal system and the cerebello-thalamo-cortical or dentate-rubro-olivary pathways

## Features

- **Irregular low frequency (4.5 Hz) tremor**, mostly of the upper extremities and affecting both proximal and distal muscles
- It **presents at rest** and is **aggravated by positioning and movement (combination of resting, postural and action tremor)**
- Signs of ataxia and weakness can occur

## Differential diagnosis:

- Holmes tremor VS Parkinson In contrast to Holmes tremor, Parkinsonian resting tremor (4-6 Hz) improves with voluntary activity and involves distal muscles.

## Treatment

- Initial medical therapy: levodopa
- For refractory cases: thalamotomy or chronic thalamic stimulation

# Chorea

Chorea describes **involuntary**, **rapid**, **jerky** movements which often **move** from one part of the body to another.
Chorea is caused by damage to the **basal ganglia**, especially the **caudate nucleus**.
Slower, sinuous movement of the limbs is termed athetosis.

## Causes of chorea:

- **Huntington's disease**, **Wilson's disease**, **Ataxic telangiectasia.**
- Rheumatic fever: Sydenham's chorea.

- SLE, anti-phospholipid syndrome, vasculitis (PAN, Behcet's disease).
- Drugs: oral contraceptive pill, L-dopa, antipsychotics.
- Pregnancy: chorea gravidarum.
- Thyrotoxicosis.
- Neuro-acanthocytosis.
- Polycythaemia rubra vera.
- **CO poisoning,** cyanide, opiates, mercury.
- Cerebrovascular disease.

**Tetrabenazine** works as a **VMAT-inhibitor** (vesicular monoamine transporter-2), involved in transportation of monoamines. It is indicated for **Huntington's chorea** to reduce hyperkinetic movements.

## Hemiballism

Hemiballism occurs following damage to the **subthalamic nucleus**.

Ballisic movements are **involuntary**, **sudden**, **jerking, severe** flinging movements **following no particular pattern** which occur **contralateral** to the side of the lesion.

The ballisic movements primarily affect the **proximal limb musculature** whilst the distal muscles may display more choreiform-like movements.
Symptoms may decrease whilst the patient is asleep.

### Aetiology:

- Stroke in elderly, with arteriosclerotic risk factors including HTN, DM, IHD, dyslipidaemia.
- Infection or inflammatory in young.
- hyperglycaemia

### Treatment

- tetrabenazine is the treatment of choice.
- Anti-dopaminergic agents (e.g. **Haloperidol**) are the mainstay of treatment.
- Topiramate can be used, as can intrathecal baclofen, botulinum toxin and tetrabenazine.
- Functional neurosurgery can be used for cases which have failed to respond to other treatment.

### Prognosis

- Usually the flinging movements stop spontaneously in the next 4-8 weeks

# Restless legs syndrome (RLS)

It is a syndrome of **spontaneous, continuous lower limb movements** that may be associated with **paraesthesia**.

It is extremely common, affecting between **2-10%** of the general population.

Males and females are **equally** affected and a **family history** may be present.

## Clinical features:

- **Uncontrollable urge to move legs** (akathisia). Symptoms initially occur at **night** but as condition progresses may occur during the day. Symptoms are worse at rest.
- **Paraesthesias** e.g. 'crawling' or 'throbbing' sensations.
- Movements during sleep may be noted by the **partner** - periodic limb movements of sleeps (PLMS).

## Causes and associations:

- There is a positive **family history in 50%** of patients with **idiopathic** RLS.
- **Iron deficiency anaemia.**
- Uraemia
- DM
- Pregnancy

The diagnosis is clinical although **bloods to exclude iron deficiency anaemia may be appropriate (as Ferritin).**

## Management:

- Simple measures: **walking**, stretching, massaging affected limbs.
- **Treat any iron deficiency.**
- **Dopamine agonists** are first-line treatment (e.g. **Ropinirole**, Pramipexole, and Rotigotine).
- Benzodiazepines.
- Gabapentin.

**EX:** A 67-year-old woman comes for review with her husband. Her husband complains that she is constantly getting up from bed at night and pacing around the bedroom. She complains of 'antsy' legs and a 'horrible, creeping sensation'. Her symptoms generally come on in the evening and are only relieved by moving round. >>> Restless legs syndrome (**RLS**) >> **Treatment**: **Ropinirole.**

# Neuroleptic malignant syndrome (NMS)

It is a **rare** but **dangerous** condition seen in patients taking **antipsychotic** medication (e.g., Olanzapine haloperidol, chlorpromazine).

It carries a mortality of up to 10% and can also occur with **atypical antipsychotics**.

It may also occur with **dopaminergic drugs (such as levodopa)** for **Parkinson's** disease, usually when the **drug is suddenly stopped** or **the dose reduced**.

It is thought to arise from blockage of dopamine receptors or decrease in availability of dopamine (**↓ Dopamine**).

Primary diagnostic features are altered conscious level, autonomic instability and muscular rigidity with raised CPK

The syndrome can occur **within hours** of initiating drug therapy, but typically takes about **1 week**.

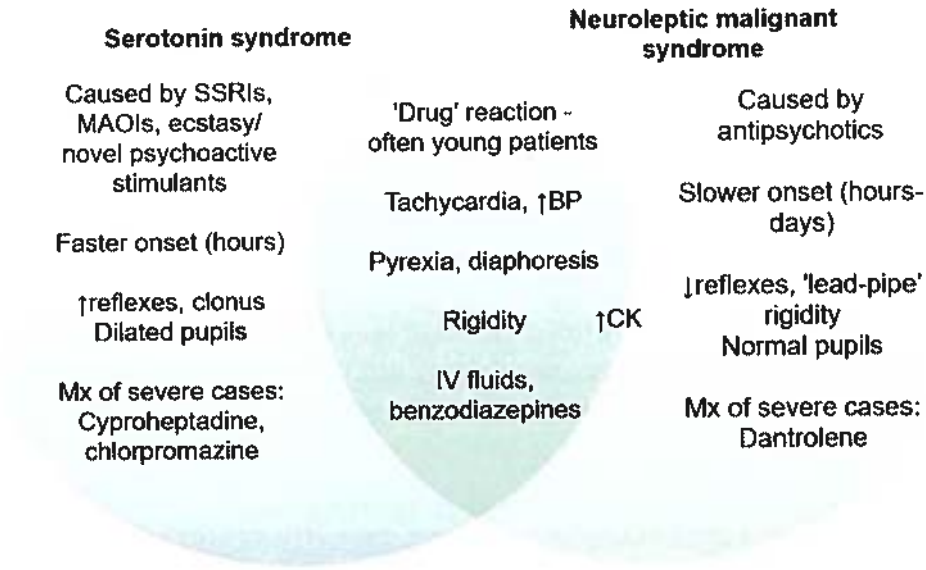
The mortality is between 10-20%.

## Features:

- More common in **young male** patients
- **Onset** usually in **first 10 days of treatment** or **after increasing dose of** antipsychotic.
- **Pyrexia**
- **Altered mental status**
- **Muscle rigidity** (sometimes with dysphagia and dysarthria).
- **Extrapyramidal signs, tremors, catatonia, muteness.**
- **Tachycardia**
- **Autonomic dysfunction.**
- A raised **CPK** & **AST** is present in most cases.
- A **leucocytosis** may also be seen.
- **Renal failure** may occur secondary to **rhabdomyolysis**
- **Metabolic acidosis.**
- **DIC.**

## Management:

- stop antipsychotic
- patients should be transferred to a medical ward if they are on a psychiatric ward and often they are nursed in intensive care units
- IV fluids to prevent renal failure
- **dantrolene** may be useful in selected cases
  - thought to work by decreasing excitation-contraction coupling in skeletal muscle by binding to the ryanodine receptor, and decreasing the release of calcium from the sarcoplasmic reticulum
- bromocriptine, dopamine agonist, may also be used




Venn diagram showing contrasting serotonin syndrome with neuroleptic malignant syndrome. Note that both conditions can cause a raised creatine kinase (CK) but it tends to be more associated with NMS.

**Dantrolene** is thought to work by decreasing excitation-contraction coupling in skeletal muscle by binding to the ryanodine receptor, and decreasing the release of calcium from the sarcoplasmic reticulum.

**EX:** A 35-year-old man with a history of schizophrenia is brought to the ED by worried friends due to drowsiness. On examination he is generally rigid. >>> A diagnosis of neuroleptic malignant syndrome should be suspected.

# Multiple system atrophy

**Shy-Dragger syndrome** is a type of multiple system atrophy.

## Features:

- **Parkinsonism**
- **Cerebellar** signs (e.g., ataxia, tremor, dysarthria)
- **Autonomic disturbance** (**disturbance of sphincter control, atonic bladder with urinary retention, impotence, anhidrosis** and **postural hypotension**)

The Parkinson's symptoms associated with multi-system atrophy respond **poorly** to dopamine agonists or L-dopa, in contrast to idiopathic Parkinson's.

Urinary retention can be managed with an **indwelling catheter** if required.

Postural hypotension managed with **support stockings ± mineralocorticoids**

## Corticobasal degeneration

- Dementia
- Asymmetric motor abnormalities, often initially affecting only one limb
- **Alien limb phenomenon**: involuntary but purposeful movement of the limb PLUS feeling that the affected limb does not belong to the patient and acts on its own

### Differential diagnoses of Parkinson-plus syndromes

| Multiple system atrophy | Progressive supranuclear palsy | Corticobasal degeneration | Dementia with Lewy bodies |
|---|---|---|---|
| • Lewy bodies<br>• **Autonomic dysfunction with urogenital problems** | • **Vertical gaze palsy**<br>• Frontal lobe disturbances | • Asymmetric motor symptoms<br>• **Alien limb phenomenon** | • Lewy bodies<br>• **Visual hallucinations** |

# Alzheimer's disease (AD)

Alzheimer's disease is a **progressive degenerative disease of the brain** accounting for the majority of dementia seen in the UK.
Alzheimer's disease is characterised **early** in the disease by **short term memory loss.**

## Genetics:

- Most cases are sporadic
- 5% of cases are inherited as an **autosomal dominant** trait.
- **Mutations** in the amyloid precursor protein (chromosome 21), presenilin 1 (chromosome 14) and presenilin 2 (chromosome 1) genes are thought to cause the inherited form.
- Apoprotein E allele E4 - encodes a cholesterol transport protein.

## Pathological changes:

- **Macroscopic** = widespread cerebral atrophy, particularly involving the cortex and hippocampus.
- **Microscopic** = intraneuronal neurofibrillary tangles, neuronal plaques, deficiency of neurons.
- **Biochemical** = deposition of type A-Beta-amyloid protein in cortex, deficit of Ach from damage to an ascending forebrain projection.

## Neurofibrillary tangles:

- Paired helical filaments are partly made from a protein called tau
- In AD are tau proteins are excessively phosphorylated

## Management:

- NICE now recommend the **three acetyl cholinesterase inhibitors (↑Ach)**: **(Donepezil (Aricept®), Rivastigmine (Exelon®)** and **(Galantamine)** as options for managing mild to moderate Alzheimer's disease.
- **Memantine (Namenda®):** (a NMDA receptor antagonist) is reserved for patients with moderate - severe Alzheimer's.

Donepezil → SE: **Insomnia**, **Bradycardia**, **Heart block** and **UB obstruction**

The NICE guidelines recommend discontinuation of cholinesterase inhibitors as Donepezil once the mini mental state examination has fallen below 12/30 and possibly consider Memantine, which is licensed for use in moderate to severe dementia.
So pt. **with Dementia on Donepezil (Aricept®)**, then ↓ **MMSE** >>> so **withdraw Donepezil and consider Memantine.**

**Non-pharmacological:** should always be attempted prior to resorting to pharmacologic treatment.

- **Memory therapy** for all dementias: involves improving cognitive abilities through image recognition, solving math problems, and past memory recall.
- Behavioral and environmental regulation, such as:
- **adhering to a regular sleep schedule**
- Maintaining a consistent environment will help orient the patient. Frequent travel has been shown to worsen the symptoms of Alzheimer's disease

## Lewy body dementia (LBD)

Lewy body dementia is an increasingly recognised cause of dementia, accounting for up to **20%** of cases.

It is a **mixture** of Alzheimer's disease with Parkinson's disease.

The characteristic pathological feature is alpha-synuclein **cytoplasmic inclusions (Lewy bodies)** in the substantia nigra, paralimbic and neocortical areas.

The relationship between Parkinson's disease and Lewy body dementia is **complicated**, particularly as dementia is often seen in Parkinson's disease.

Also, **up to 40% of patients with Alzheimer's have Lewy bodies**.

**Neuroleptics** should be **avoided** in Lewy body dementia as patients are extremely sensitive and may develop irreversible Parkinsonism.

Questions may give a history of a patient who has deteriorated following the introduction of an antipsychotic agent (like haloperidol).

**EX:** A 64-year-old man who is under investigation for parkinsonian symptoms is brought to the GP by his wife. She is concerned her husband is becoming increasingly agitated. The GP prescribes **haloperidol**. One week later the parkinsonian symptoms have deteriorated markedly. What is the most likely underlying diagnosis? >>> Lewy body dementia.

### Features:

- **Progressive cognitive impairment.**
- **Parkinsonism.**

- **Hallucinations** (**visual** or non-visual hallucinations, other features such as delusions may also be seen).
- **Symptoms worsen with neuroleptics/ antipsychotic agent.**
- **Myoclonus**

## Diagnosis:

- Usually, **clinical**.
- **S**ingle-**p**hoton **e**mission **c**omputed **t**omography (**SPECT**) is increasingly used. It is currently commercially known as a **DaTscan (dopamine transporter scan)**.
  - Dopaminergic iodine-123-radiolabelled 2-carbomethoxy-3-(4-iodophenyl)-N-(3-fluoropropyl) nortropane (123-I FP-CIT) is used as the radioisotope.
  - The sensitivity of SPECT in diagnosing Lewy body dementia is around 90% with a specificity of 100%.
  - Its main drawback is expense.

The findings on conventional imaging such as MRI are generally non-specific.

Lewy body dementia has no specific identifying features on CT or MRI.

## Management

**Haloperidol is contra-indicated in Lewy body dementia**

- The treatment of choice is **rivastigmine**, which improves both the visual hallucinations, and cognitive impairment.
- **Neuroleptics should be avoided in Lewy body dementia**, as patients are extremely sensitive and may develop irreversible parkinsonism.
  - Questions may give a history of a patient who has deteriorated following the introduction of an antipsychotic agent
  - The most appropriate therapeutic strategy with respect to maintaining his mobility is → **Stop dopamine-blocking drugs (causing significant parkinsonism) eg: quetiapine**

**A 78-year-old man with memory impairment, hallucinations, resting tremor, festinating gait and an expressionless face. He scores 12 / 30 on the mini-mental state examination (MMSE). which test is most likely to confirm the diagnosis?** **>> SPECT scan** (Lewy body dementia)

**H/O parkinsonian symptoms + agitation. deteriorated after prescribing haloperidol. What is the most likely underlying diagnosis?**
**>> Lewy body dementia**

# Frontotemporal dementia

## Overview

- Frontotemporal dementia is an umbrella term for a group of brain disorders that primarily affect the frontal and temporal lobes of the brain.
- These areas of the brain are generally associated with personality, behavior and language.
- In frontotemporal dementia, portions of these lobes shrink (atrophy).
- Signs and symptoms vary, depending on which part of the brain is affected.
- Some people with frontotemporal dementia have dramatic changes in their personalities and become socially inappropriate, impulsive or emotionally indifferent, while others lose the ability to use language properly.
- Frontotemporal dementia can be misdiagnosed as a psychiatric problem or as Alzheimer's disease.
- But frontotemporal dementia tends to occur at a younger age than does Alzheimer's disease.
- Frontotemporal dementia often begins between the ages of 40 and 65 but occurs later in life as well.
- FTD is the cause of approximately 10% to 20% of dementia cases.

## Symptoms

- Signs and symptoms of frontotemporal dementia can be different from one individual to the next.
- Signs and symptoms get progressively worse over time, usually over years.
- Clusters of symptom types tend to occur together, and people may have more than one cluster of symptom types.

## Behavioural changes

**The most common signs of frontotemporal dementia involve extreme changes in behavior and personality. These include:**

- Increasingly inappropriate social behavior
- Loss of empathy and other interpersonal skills, such as having sensitivity to another's feelings
- Lack of judgment

- Loss of inhibition
- Lack of interest (apathy), which can be mistaken for depression
- Repetitive compulsive behavior, such as tapping, clapping or smacking lips
- A decline in personal hygiene
- Changes in eating habits, usually overeating or developing a preference for sweets and carbohydrates
- Eating inedible objects
- Compulsively wanting to put things in the mouth

## Speech and language problems

- Some subtypes of frontotemporal dementia lead to language problems or impairment or loss of speech.
- Primary progressive aphasia, semantic dementia and progressive agrammatic (nonfluent) aphasia are all considered to be frontotemporal dementia.

### Problems caused by these conditions include:

- Increasing difficulty in using and understanding written and spoken language, such as having trouble finding the right word to use in speech or naming objects
- Trouble naming things, possibly replacing a specific word with a more general word such as "it" for pen
- No longer knowing word meanings
- Having hesitant speech that may sound telegraphic
- Making mistakes in sentence construction

## Motor disorders

- Rarer subtypes of frontotemporal dementia are characterized by problems with movement similar to those associated with Parkinson's disease or amyotrophic lateral sclerosis (ALS).

### Motor-related problems may include:

- Tremor
- Rigidity
- Muscle spasms or twitches
- Poor coordination
- Difficulty swallowing
- Muscle weakness
- Inappropriate laughing or crying
- Falls or walking problems

## Causes

- In frontotemporal dementia, the frontal and temporal lobes of the brain shrink.
- In addition, certain substances accumulate in the brain.
- What causes these changes is usually unknown.
- There are genetic mutations that have been linked to frontotemporal dementia.
- But more than half of the people who develop frontotemporal dementia have no family history of dementia.
- Recently, researchers have confirmed shared genetics and molecular pathways between frontotemporal dementia and amyotrophic lateral sclerosis (ALS).
- More research needs to be done to understand the connection between these conditions, however.

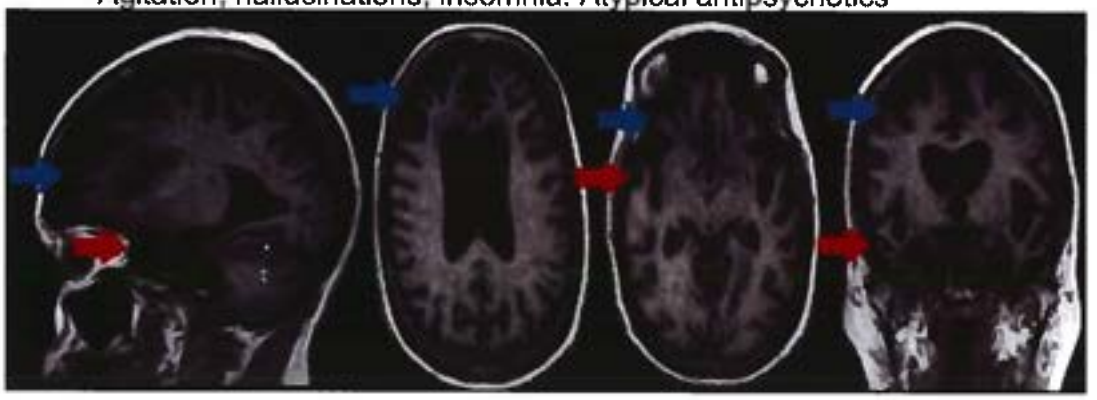
## Risk factors

- Your risk of developing frontotemporal dementia is higher if you have a family history of dementia.
- There are no other known risk factors.

Patients with FTD display changes of personality and social behavior, but their memory generally remains intact.

## Treatment

- No curative treatment.
- Cholinesterase inhibitors and memantine are usually not effective
  Agitation, hallucinations, insomnia: Atypical antipsychotics



Frontotemporal dementia has atrophy of the bilateral frontal (blue arrows) and temporal (red arrows) lobes that can be seen withthese T1-weighted MRI images

## Normal pressure hydrocephalus

It is a reversible cause of dementia seen in elderly patients.

It is thought to be secondary to reduced CSF absorption at the arachnoid villi.

These changes may be secondary to head injury, subarachnoid haemorrhage or meningitis.

### A classical triad of features is seen:

- **Dementia** and bradyphrenia
- **Urinary incontinence**
- **Gait abnormality**: as if he is learning how to walk.

**Urinary incontinence + gait abnormality + dementia = normal pressure hydrocephalus.**

### Diagnosis

**Imaging: Hydrocephalus** with an **enlarged fourth ventricle.**

**Management: VPS** (Ventriculo-peritoneal shunting).

## Creutzfeldt – Jakob Disease (CJD)

- In the majority of the cases the first symptoms are **psychiatric (depression, irritability, anxiety, withdrawal and dysphonia) and painful sensory symptoms in the LLs.** are the most common presenting features
- **Rapidly progressive**, severe invariably **fatal** usually within few months.
- **Dementia.**
- **Cerebellar ataxia.**
- Diffuse **myoclonic jerks**: it is typical and progressive, even during the later stage when the patient is stuporous or comatose.
- Ataxia and involuntary movements (for example, myoclonus) usually appear at an interval of about **6 months after the initial symptoms**.
- **New variant CJD** usually presents in a young person, in their twenties or thirties.
- EEG is usually normal in new variant CJD.

- **Rapid cognitive decline** in a **young** person with **myoclonus** is strongly suggestive of Creutzfeldt-Jakob disease (CJD).

## Investigations:

- **EEG**: characteristic diffuse non-specific slowing **periodic high amplitude sharp wave complexes PSWCs** of 1-2 Hz, but diagnosis relies on either specialized tests for prion protein in CSF **or brain biopsy**.
- **MRI**: **Pulvinar sign** > 90% (**bilateral posterior thalamic nuclei high signal** abnormalities) **pathological** in **variant CJD** (not sporadic).
- **CSF**:14-3-3 protein
- **Prion protein** in tonsils.

## Sporadic CJD:

- It is a prion disease.
- Normal prion proteins are found on cell surfaces all over the body mainly in an alpha helix structure.
- Predominantly affects late **mid** aged individuals with mean age of death in the **late 60s**.
- **Memory impairment** and subsequently **rapidly progressive dementia** from few weeks duration to less than 2 years.
- Commonly accompanying features include **cerebellar ataxia, pyramidal** and **extrapyramidal signs** and **myoclonus** which are common early features.
- A definitive diagnosis can only be made post-mortem.
- The median duration of illness is 4 months and about 65% of cases die within 6 months.

**EX**: Male pt. 60 years with increasing forgetfulness over the **last 3 months**, he become more agitated and police brought him home after seeing him wondering in the street, O/E: he has broad based gait, intention tremor, past pointing, myoclonic jerk, brisk reflexes and bilateral up-going plantars >>> **Sporadic CJD**.

## Treatment

- No curative treatment.

# Transient global amnesia (TGA)

- It represents a transient vascular insufficiency of both hippocampi.
- This is a rare condition which usually affects people **over the age of 50.**
- It lasts **less than 24 hours** and an **awareness of personal identity** is retained, along with **normal cognition**.
- patients may **appear anxious** and **repeatedly ask the same question**
- patients have no recall of events after the attack

**The cause** is **unknown** but it may be related to a migrainous phenomenon or transient ischemia

It is claimed that the condition may be associated with neuronal loss in the hippocampal area or abnormal metabolism by neurones in this area leading to build up of lactate, but definitive proof does not exist.

## Investigations

- If the diagnosis is clear, further diagnostic procedures are not necessary.
- If the diagnosis is uncertain:
  - MRI: evidence of typical focal, hyperintense lesions in the hippocampus
  - EEG: exclude differential diagnoses (e.g., epileptic amnesic attacks)

## Treatment: is Reassurance.

**No** specific therapy is required; specifically, **no** increased use of anti-platelet agents is needed.

## Prognosis

- Resolves spontaneously within 24 hours
- Recurrence is unusual

**EX:** A 60-year-old man presents with an episode of memory loss.
Three days earlier he had become **confused**. His wife led him into the house - he apparently sat down at her request, and had a cup of tea. **He then wandered around the house**, **confused**, **but remained conscious** and able to have some **conversation with his wife**, though continuing to **ask similar questions repeatedly.**
**After 3 hours**, he abruptly **returned to normal** and had **no recollection** of the events.

# Herpes simplex encephalitis (HSE)

Herpes simplex (HSV) encephalitis is a very common topic in the exam.

The virus characteristically affects the **temporal** lobes - questions may give the result of imaging or describe temporal lobe signs e.g. aphasia.

## Features:

- **Fever, headache,** vomiting.
- **Psychiatric symptoms, change in personality, odd behaviour, becoming aggressive over trivial things, confusion, seizures.**
- **Focal** features e.g. **aphasia.**
- Peripheral lesions (e.g. cold sores) have no relation to presence of HSV encephalitis.

## Pathophysiology:

- HSV-1 responsible for 95% of cases in adults
- Typically affects temporal and inferior frontal lobes

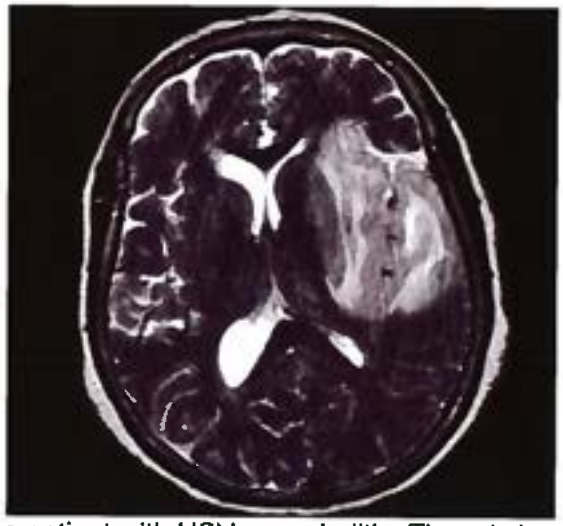
## Investigations:

- CSF: **lymphocytosis**, elevated protein
- **PCR for HSV** (the quickest method).
- CT/ MRI (**MRI** is better): **medial temporal** and **inferior frontal** changes (e.g. **petechial haemorrhages**), low attenuation areas with surrounding oedema - normal in one-third of patients.
- **EEG**: **lateralised periodic discharges** at **2 Hz** (**BUT** is **not** diagnostic).

**Treatment:** **I.V Acyclovir** (10-15 mg/kg IV every 8 hrs for **10-14 days**).

## Prognosis

- The **prognosis** is dependent on whether **acyclovir** is commenced **early**.
- If treatment is started promptly the mortality is 10-20%.
- Left untreated the mortality approaches 80%.



MRI of a patient with HSV encephalitis. There is hyperintensity of the affected white matter and cortex in the medial temporal lobes and insular cortex.

**EX**: A 34-year-old woman who presents with confusion, headache and fever is admitted to the ER. Shortly after admission she has a seizure. A MRI scan is performed which shows patchy haemorrhagic changes in the temporal lobe. Given the likely diagnosis, what is the treatment of choice? **I.V Acyclovir**

## Wernicke's encephalopathy

Wernicke's encephalopathy is a **neuropsychiatric** disorder caused **by thiamine deficiency** which is most commonly seen in **alcoholics**.

It is caused by lesions in the medial thalamic nuclei, mammillary bodies, periaqueductal and periventricular brainstem nuclei and superior cerebellar vermis.

Rarer causes include: persistent vomiting, stomach cancer, dietary deficiency and after bariatric surgery.

A classic **triad** of **Confusion, ataxia ( evident by ataxic gain and nystagmus)**, and **Ophthalmoplegia**.

In Wernicke's encephalopathy **petechial haemorrhages** occur in a variety of structures in the brain including the mammillary bodies and ventricle walls.

**Features** (wide variety of presentations):

- **Confusion**, altered GCS.
- **Nystagmus** (the most common ocular sign).
- **Ataxia**.
- **Ophthalmoplegia.**
- Peripheral sensory neuropathy.
- Impairment of **short** term **memory**.

It is worth noting that beside a wide variety of presentation, it is Is common in elderly malnourished or bedridden patients, and must be suspected and empirically treated with thiamine in any patient with unexplained cause of altered sensorium.

## Investigations:

- **1st investigations to order ► therapeutic trial of parenteral thiamine**
- Decreased red cell transketolase.
- MRI.

**Treatment**: It is a medical emergency, requiring **urgent IV thiamine 50 mg IV**.

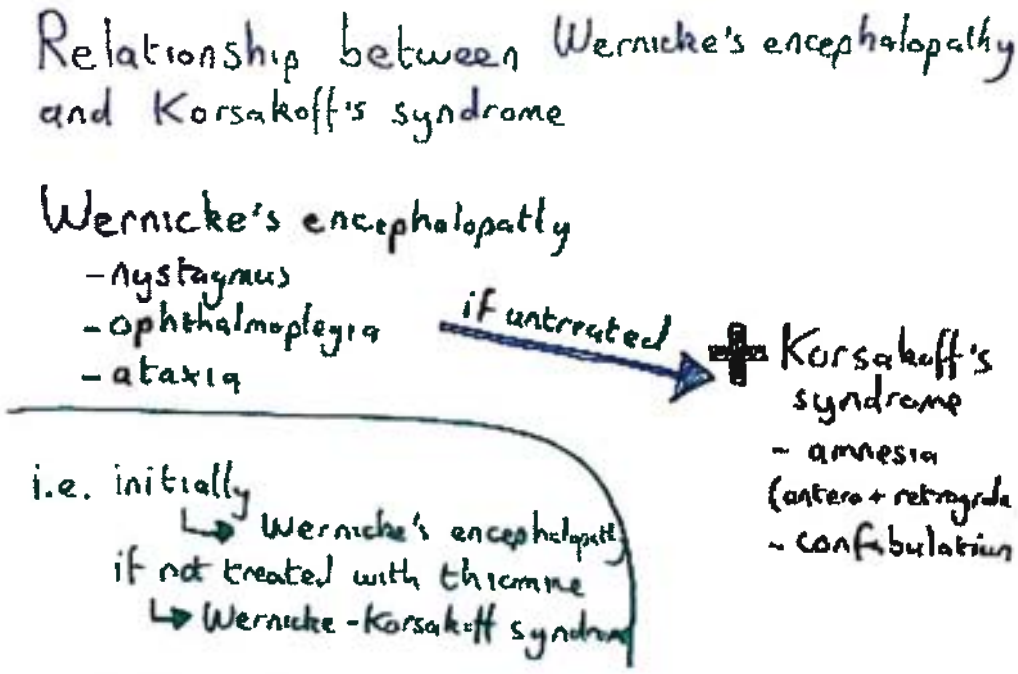
The episode of Wernicke's encephalopathy may be precipitated by **IV dextrose** administration which exhaust his vitamin B reserves, hence **B vitamins must be administered** to **all alcoholic** patients requiring **dextrose**.

**Alcohol** is a common cause of **hypoglycaemia**, and can be rapidly life-threatening if not recognised. Common initial symptoms are tachycardia and sweating. RBS should be checked in all patients who become acutely unwell.

**N.B:** Inability to acquire **new memories** with subsequent compensatory **confabulation** by the patient >>> suggests the development of **Korsakoff's amnesic syndrome**:

Other symptoms may include: Delirium, Anxiety, Fear, Depression, Confusion, Delusions, Insomnia, Painful extremities, sometimes bilateral wrist drop but more frequently bilateral foot drop with pain or pressure over the long nerves.

**Marchiafava Bignami Syndrome**: Corpus callosum degeneration from chronic alcohol excess.




## Brain tumours

### Type & Features

#### Glioblastoma multiform

- **The most common primary brain tumour in adults, accounts for about 20% of all cerebral tumours.**
- Histology: Pleomorphic tumour cells border necrotic areas
- **Pseudo palisading tumour cells on brain biopsy are a characteristic**

#### Meningioma

- The second most common primary brain tumour in adults
- Histology: Spindle cells in concentric whorls and calcified psammoma bodies

#### Schwannoma

- Often seen in the cerebellopontine angle: acoustic neuroma
- Bilateral schwannoms are seen in neurofibromatosis
- Histology: Antoni A or B patterns are seen. Verocay bodies (acellular areas surrounded by nuclear palisades)

#### Pilocytic astrocytoma

- The most common primary brain tumour in children
- Histology: Rosenthal fibres (corkscrew eosinophilic bundle)

### Medulloblastoma

- More common in children
- Found exclusively in the posterior fossa
- Metatases through the CSF
- Histology: Small, blue cells. Rosette pattern of cells with many mitotic figures

### Ependymoma

- Commonly seen in the 4th ventricle
- May cause hydrocephalus
- Histology: perivascular pseudorosettes

### Oligodendroma

- Benign, slow-growing tumour common in the frontal lobes
- Histology: Calcifications with 'fried-egg' appearance

### Haemangioblastoma

- Vascular tumour of the cerebellum
- Associated with von Hippel-Lindau syndrome
- Histology: foam cells and high vascularity

### Pituitary adenoma

- Most common type is a prolactinoma
- May present with bitemporal hemianopia

### Craniopharyngioma

- Most common paediatric supratentorial tumour
- Histology: Derived from remnants of Rathke pouch
- The commonest presentation in young patients is growth failure and delayed puberty.
- CT: suprasellar calcified cyst.

### Metastases

- Most common type of brain tumour
- The most common sites that metastasise to the brain is **lung (44%)**, therefore, **a chest x -ray would be the initial investigation of choice**
- Initial treatment: Start dexamethasone immediately

## Brain abscess

Brain abscesses may result from a number of causes including, **extension of sepsis from middle ear or sinuses,** trauma or surgery to the scalp, penetrating head injuries and embolic events from endocarditis

The presenting symptoms will depend upon the site of the abscess (those in critical areas e.g. motor cortex) will present earlier. Abscesses have a considerable mass effect in the brain and raised intracranial pressure is common.

- **Headache:** often dull, persistent
- **fever:** may be absent and usually not the swinging pyrexia seen with abscesses at other sites
- **focal neurology:** e.g., oculomotor nerve palsy or abducens nerve palsy secondary to raised intracranial pressure
- other features consistent with raised intracranial pressure
  - nausea.
  - Papilledema.
  - Seizures.

**Investigations:** Assessment of the patient includes imaging with CT scanning

### Management

- surgery
  - a craniotomy is performed and the abscess cavity debrided
  - the abscess may reform because the head is closed following abscess drainage.
- IV antibiotics: **IV 3rd-generation cephalosporin + metronidazole**
- intracranial pressure management: e.g. dexamethasone

## Acute disseminated encephalomyelitis

- Acute disseminated encephalomyelitis (ADEM) is an autoimmune demyelinating disease of the central nervous system.
- It may also be termed post-infectious encephalomyelitis.
- The etiology is not fully understood and it can occur following infection with a bacterial or viral pathogen.

- Common infections include measles, mumps, rubella and varicella; however, this list is not exhaustive.
- After a lag time of between a few days to 2 months, there is an acute onset of multifocal neurological symptoms with rapid deterioration.
- Non-specific signs such as headache, fever, nausea and vomiting may also accompany the onset of illness.
- Motor and sensory deficits are frequent and there may also be brainstem involvement including oculomotor defects.
- There are no specific biomarkers for the diagnosis of ADEM.
- MRI imaging may show areas of supra and infra-tentorial demyelination.
- Management involves intravenous glucocorticoids and the consideration of IVIG where this fails.

## Anti-NMDA receptor encephalitis

- Anti-NMDA receptor encephalitis is a paraneoplastic syndrome, presenting as prominent psychiatric features including agitation, hallucinations, delusions and disordered thinking; seizures, insomnia, dyskinesias and autonomic instability.
- Ovarian teratomas are detected in up to half of all female adult patients, particularly prevalent in Afro-Caribbean patients.
- MRI head can be normal but abnormalities can be visualised on FLAIR sequences in the deep subcortical limbic structures.
- CSF may demonstrate pleocytosis but can be normal initially.
- Anti-MuSK is an autoantibody specific to muscle kinase in myasthenia gravis with no evidence of a thymoma and without antibodies to acetylcholine receptors.
- Anti-GM1 is an autoantibody specific to acute inflammatory demyelinating polyneuropathy (AIDP) variant of Guillain-Barre syndrome.

### Treatment

- immunosuppression with intravenous steroids, immunoglobulins, rituximab, cyclophosphamide or plasma exchange, alone or in combination.
- Resection of teratoma is also therapeutic.

## Arnold-Chiari malformation

Arnold-Chiari malformation describes the downward displacement, or herniation, of the cerebellar tonsils through the foramen magnum. Malformations may be congenital or acquired through trauma.

### Features

- non-communicating hydrocephalus may develop as a result of obstruction of cerebrospinal fluid (CSF) outflow
- headache
- syringomyelia

### Investigations

- **MRI brain: >> Narrow posterior fossa**

### Treatment

- type II and III CM and in symptomatic type I CM
  - Surgery
- asymptomatic type I CM:
  - Surveillance: annual MRI of the brain to look for development of syringomyelia and/or hydrocephalus.

## Acute confusional state (Delirium)

Acute confusional state is also known as delirium or acute organic brain syndrome.
It affects up to **30%** of **elderly** patients **admitted** to hospital.

### Features - wide variety of presentations:

- Memory disturbances (loss of short term > long term)
- May be **very agitated** or withdrawn
- Disorientation
- Mood change
- Visual hallucinations
- Disturbed sleep cycle
- Poor attention

### Diagnosis

- The **C**onfusion **A**ssessment **M**ethod (**CAM**) is the most effective tool in identifying delirium.
  If there is difficulty distinguishing between the diagnoses of delirium, dementia or delirium Superimposed on dementia, treat for delirium first

## Management:

- Treatment of underlying **cause**
- **Modification of environment**
- The 2006 Royal College of Physicians publication 'the prevention, diagnosis and management of delirium in older people: concise guidelines' recommended **haloperidol 0.5 mg** as the first-line sedative.
- The 2010 NICE delirium guidelines advocate the use of **haloperidol** or **olanzapine.**
- Agitation should initially be managed with nonpharmacologic strategies, verbal and non- verbal techniques to de-escalate the situation (e.g., **modification of environment**). Medications should be reserved for refractory agitation.
- Avoid antipsychotic drugs in Parkinson's disease or dementia with Lewy bodies

**N.B:** Whilst many doctors may use oral lorazepam in this situation the Royal College of Physicians recommend haloperidol as the first-line sedative.

# Dementia

Dementia is thought to affect over 700,000 people in the UK and accounts for a large amount of health and social care spending.

The **most common cause of dementia** in the UK is **Alzheimer's disease** followed by **vascular** and **Lewy body dementia**. They may coexist.

**DP43 is a protein that has recently been found to be involved in a multitude of neurodegenerative diseases** including **dementia** and motor neuron disease.

## Common causes of dementia

- **Alzheimer's disease** (> 50% of dementia cases)
- multi-infarct dementia due to **cerebrovascular disease** (20% of dementia cases):
- Lewy body dementia (c.10-20%)

### Rarer causes (c. 5% of cases)

- Huntington's
- CJD
- Pick's disease (atrophy of frontal and temporal lobes)
- HIV (50% of AIDS patients).

## Features

- mini-mental state examination. A score of 24 or less out of 30 suggests dementia
- Short term memory impairment is the commonest clinical presentation of Alzheimer's disease. **The best way to test short term memory is to ask the patient to recall new information in the next few minutes.**
- Long term memory is usually intact.
- Usually patients are fully orientated in time, person and place.

### Distinguishing between normal aging and dementia

- Memory impairment, occasional difficulties in word finding, and slower cognitive processing are normal effects of aging.
- An important distinguishing factor between normal aging and forms of dementia is the degree to which independence with everyday activities is impaired. In normal aging, **independence in daily activities** is preserved.
- cognitive exams are within normal limits in aging.
- **Alzheimer's disease is often accompanied by behavioral changes (such as aggression, depression, insomnia)**

## Investigations

### Vascular dementia

- Typically occurs in those with widespread vascular disease. A history of strokes or the presence of focal neurological signs are very suggestive
- CT or MRI will show multiple lacunar infarcts
- Does not respond to acetylcholinesterase inhibitors such as donepezil.
- Vascular dementia caused by lipohyalinosis or microatheroma formation and NOT thromboemboli. Therefore, anticoagulation is not indicated.

Memory therapy is the best next step in management for patient's confirmed vascular dementia.

## Management:

- In primary care a **blood screen** is usually sent to exclude reversible causes (e.g., Hypothyroidism).
- Single-photon emission computed tomography **(SPECT) should be used to differentiate, Alzheimer's disease, vascular dementia and frontotemporal dementia if the diagnosis is in doubt.**
- Cerebrospinal fluid examination should be used if Creutzfeldt-Jakob disease or other forms of rapidly progressive dementia are suspected.

NICE recommend the following tests: **CBC**, **U&E**, **LFTs**, **Ca++**, **glucose**, **TFTs**, **Vit.B12** and **folate** levels. Patients are now commonly referred on to old-age psychiatrists (sometimes working in **'memory clinics'**).

- In secondary care **neuroimaging** is performed* to exclude other reversible conditions (e.g. Subdural haematoma, normal pressure hydrocephalus) and help provide information on aetiology to guide prognosis and management.

Neuroimaging is required to diagnose dementia

## Myasthenia gravis (MG)

Myasthenia gravis is an acquired humoral autoimmune disorder resulting in insufficient functioning **acetylcholine receptors**.

**A**cetyl **ch**oline **R**eceptors **A**uto **A**nti**b**odies (**ACHRAB**) are seen in **90%** of cases (antibodies are less commonly seen in disease limited to the ocular muscles).

These antibodies block Ach receptors at the **post-synaptic** neuromuscular junction.

It is well known to be associated **with other autoimmune diseases** such as **pernicious** anaemia, **thyroid** disease and **rheumatoid arthritis**.

Myasthenia is more common in women (2:1).

It is a neuromuscular disease leading to **fluctuating** muscle weakness & fatigability.

**The key feature is muscle fatigability** - muscles become **progressively** weaker during periods of activity **later in the day** after prolonged use of specific muscle and slowly improve after periods of rest:

1) **Proximal muscle weakness**: face, neck, limb girdle.
2) **Extra ocular muscle weakness**: **diplopia** and **Ptosis.**
3) **Dysphagia** (worse with **liquids** than solids).
4) **Dysarthria**, slurred speech.

**Associations:**

- Thymomas in 15%
- Thymic hyperplasia in 50-70%
- Autoimmune disorders: Autoimmune thyroid disorders, RA, SLE, pernicious anaemia.

30-40% of Thymoma cases have coexistent myasthenia gravis.
Thymoma has equal sex distribution and rarely presents < age of 20 years.

## Exacerbating factors:

The most common exacerbating factor is exertion resulting in fatigability, which is the hallmark feature of MG.

Symptoms become more marked during the day.

**The following drugs may exacerbate myasthenia:**

- **Penicillamine**
- Procainamide
- Quinidine
- **Beta-blockers**
- Lithium
- Phenytoin
- antibiotics: gentamicin, macrolides, quinolones, tetracyclines

## Investigations:

- **single fibre EMG**: high sensitivity (92-100%)
- **CT thorax to exclude thymoma**
- CK normal
- **autoantibodies**: around 85-90% of patients have antibodies to acetylcholine receptors.
  - In the remaining patients, about about 40% are positive for anti-muscle-specific tyrosine kinase antibodies
- **Tensilon test:** IV edrophonium reduces muscle weakness temporarily - not commonly used any more due to the risk of cardiac arrhythmia

## Management:

- long-acting acetylcholinesterase inhibitors
  - **pyridostigmine is first-line**
- immunosuppression is usually not started at diagnosis, but the majority of patients eventually require it in addition to long-acting acetylcholinesterase inhibitors:
  - prednisolone initially
  - azathioprine, cyclosporine, mycophenolate mofetil may also be used
- **thymectomy**
  - **thymectomy is not indicated if:**
    - **patients have antibodies to MUSK (muscle specific tyrosine kinase)**
    - late onset disease or
    - purely ocular disease

## Management of myasthenic crisis:

- **IVIG** (Intravenous immunoglobulins) (400mg/kg for 5 days)
- **Plasmapheresis**
- Early endotracheal intubation: **Elective intubation should be considered if the vital capacity show values are less than 20 mL / kg.**

**Myasthenic crisis:** The patient has marked respiratory weakness with reduced breath count, reduced oxygen saturation, chest expansion and forced vital capacity.

### Myasthenic crisis VS Cholinergic crisis

| | Myasthenic crisis | Cholinergic crisis |
|---|---|---|
| **Pupil** | **Normal** | **Miosis (constricted pupil)** |
| **Fasciculations** | **None** | **Presen** |
| **Heart rate** | **Tachycardia** | **Bradycardia** |
| **Skin** | **Cold and faint** | **Warm and flushed** |
| **Bronchial secretion** | **Normal** | **Increased** |

**Mechanical** dysphagia (for example, oesophageal and gastric carcinoma, oesophageal stricture, etc.) causes dysphagia that is worse with **solids** than liquids. Nasal regurgitation and dysarthria are **not** usually accompanying features of mechanical dysphagia.

**Neurogenic** dysphagia that is worse with **liquids** than solids also associated **with** dysarthria, nasal regurgitation, coughing and choking episodes during meals.

**Achalasia** typically affects **solids** more than liquids, **or both solids and liquids equally**. It typically presents at earlier age (25 to 40-years-old). Chest pain is a predominant feature, with no weight loss.

**NB: Ocular myasthenia**: **bilateral ptosis** and **variable diplopia**, without proptosis or injection of the eyes, with **normal all pupils reflexes**.

# Lambert-Eaton Myasthenic Syndrome (LEMS)

It is seen in **50 %** of cases associated with **small cell lung cancer (SCLC)**, and to a lesser extent breast and ovarian cancer.

It is a rare **paraneoplastic** phenomenon which can precede radiological evidence of the tumour by up to 5 years.

It may also occur independently as an autoimmune disorder.

## Pathophysiology

**Autoantibodies directed against presynaptic voltage-gated calcium channels** (anti- VGCC antibodies) >> ↓ Ca2 + influx >>↓ presynaptic vesicle fusion >> impaired acetylcholine release in the neuromuscular junction (NMJ)

## Features:

- **Repeated muscle contractions** after a few minutes will lead to **increased muscle strength** and **return of absent reflexes** (in contrast to myasthenia gravis).
    - In reality this is seen in only 50% of patients and following prolonged muscle use muscle strength will eventually decrease).
- **Limb girdle (proximal muscle) weakness** (affects lower limbs first).
- **Hypo-reflexia to areflexia** (but normalise with repetitive muscle contraction).
- **Autonomic** symptoms: **dry mouth**, **impotence**, difficultly micturating.
- **No** bulbar or extraocular muscle involvement like ophthalmoplegia and ptosis (unlike in myasthenia gravis).
- **No** wasting or fasciculations.
- **No** Sensory affection.

## Diagnosis:

- **EMG**: **Incremental** response to **repetitive** electrical stimulation.
- **Anti-VGCC auto Antibodies**: are found in **95%** of cases.

## Management:

- Treatment of underlying cancer.
- Immunosuppression, for example with prednisolone ± azathioprine.
- **3,4-diaminopyridine IV** is currently being trialled (works by blocking potassium channel efflux in the nerve terminal so that the action

potential duration is increased. Calcium channels can then be open for a longer time and allow greater acetylcholine release to the stimulate muscle at the end plate).

- **IVIG therapy** and **plasma exchange** may be beneficial.

**Comparison between Myasthenia gravis (MG) & Lambert-Eaton Myasthenic Syndrome (LEMS):**

| | MG | LEMS |
|---|---|---|
| **Muscle strength** | ↓ during ongoing exercise | Delayed maximum contraction |
| **Ocular muscle affection** | **Yes** | NO |
| **ANS affection** | NO | **Yes** |
| **Tendon reflexes** | Normal | ↓ with post-tetanic facilitation |
| **Single nerve stimulation (Amplitude)** | Normal | Reduced |
| **Repetitive stimulation** | ↓ at 3-Hz stimulation | Additional ↑ at 20-Hz stimulation |
| **Ach Receptor Ab** | **Positive** | ------ |
| **VGCC Ab** | -------- | **Positive** |

**Eaton** (1905-1958) U.S. neurologist at Mayo Clinic. **Lambert** (1915-2003) U.S neuro-physiologist at Mayo Clinic and Prof. of physiology at University of Minnesota.

**MRCPUK part 1 exam**: A patient of small cell lung carcinoma presents with muscle weakness, spreading from legs to arms +hyporeflexia. C/O dry mouth & erectile dysfunction. Antibodies to which one are most likely to be responsible for these findings?
**Voltage gated calcium channels**

# Myotonic dystrophy

Myotonic dystrophy (also called **dystrophia myotonica, DM**) is an **inherited myopathy** with features developing at around **20-30 years old**.

It is the most common adult muscular dystrophy.

It affects **skeletal**, **cardiac** and **smooth** muscle **+ eyes, endocrine, CNS.**

There are 2 main types of myotonic dystrophy, **DM1 and DM2.**

## Genetics:

- **Autosomal dominant**
- A **trinucleotide** repeat disorder
- DM1 is caused by a **CTG** repeat at the end of the DMPK (Dystrophia Myotonica-Protein Kinase) gene on chromosome **19**.
- DM2 is caused by a repeat expansion of ZNF9 gene on chromosome 3.

**Differences are listed in table below:The key**

| DM1 | DM2 |
|---|---|
| - DMPK gene on chromosome 19.<br>- Distal weakness more prominent. | - ZNF9 gene on chromosome 3.<br>- Proximal weakness more prominent.<br>- Severe congenital form not seen. |

## General features:

- **Myotonia** (tonic spasm of muscle) (**slow-relaxing grip** may be noticed on initial hand-shake with the patient and is typical of myotonic dystrophy).
- **Myotonic facies** (long, 'haggard' appearance).
- **Atrophy** of temporalis, masseters, facial muscle.
- **Frontal balding**
- **Bilateral ptosis**
- **Neck muscles**, including sternocleidomastoid, are involved early in the course of disease.
- **Cataracts** >> lead to **loss of red reflexes of eyes.**
- **Dysarthria** (secondary to myotonia of the tongue and pharynx).

## Other features:

- **Reduced reflexes** with myotonia
- Weakness of **arms** and **legs** (**distal** initially)
- **Mild mental / Intellectual impairment**
- **DM**
- **Testicular atrophy**
- **Cardiac** involvement: **heart block (1 st degree HB a prolonged PR interval is seen in around 20-40% of patients) or (CHB),** and **cardiomyopathy**.
- **Dysphagia**

**Dystrophia myotonica - DM1**

- Autosomal **D**ominant
- **D**istal weakness initially
- **D**iabetes
- **D**ysarthria
- **D**ysphagia

**Diagnosis** can be made on electromyogram (**EMG**) and muscle biopsy.

**EX:** A 29-year-old female with weakness in her arms, leading to increasing difficulties at work. On examination she has a bilateral ptosis and loss of the red-reflex in both eyes. Urine testing also reveals glycosuria. What is the most likely diagnosis? >> **D**ystrophia myotonica - **DM1**.

**EX**: A 27-year-old female presents complaining of generalised weakness. Examination of her face reveals bilateral ptosis, dysarthric speech and a slow-relaxing grip. What is the most likely diagnosis? >>**D**ystrophia myotonica - **DM1**.

## Treatment:

**Of myotonia: Phenytoin**

- **Ankle-foot orthosis and splints**: for foot drop.
- Lid-lifting surgery has no place as the ptosis is progressive, except in severe cases; also ± cataract extraction.

## Prognosis

- The course is chronic progressive.
- **Cardiac complications reduce life expectancy**.

# Motor neuron disease (MND

MND is a neurological condition of **unknown cause** which can present with **both UMNL** and **LMNL** signs.

**There are a number of clues which point towards a diagnosis of MND:**

- **LMN** signs in arms and **UMN** signs in legs
- **Fasciculation**
- **Wasting of the small hand muscles**/tibialis anterior is common.
- **10%** of patients with MND have **dementia** (front temporal) (**FTD**).
- **NO sensory affection** (vague sensory symptoms may occur early in the disease (e.g. limb pain) but **'never' sensory signs**).
- **NOT external ocular muscles affection.**
- **NO cerebellar signs.**
- Abdominal reflexes are usually preserved and sphincter dysfunction if present is a late feature.

Progressive **motor weakness** and **pseudo-bulbar palsy + normal sensations** + normal brain imaging >> always think of **amyotrophic lateral sclerosis. Electromyography is the best investigation** to carry out next.

'Fasciculations' >>> think MND, most commonly Amyotrophic lateral sclerosis.

It **rarely presents before 40 years** and **various 4 patterns** of disease are recognised including: amyotrophic lateral sclerosis, primary lateral sclerosis, progressive muscular atrophy and bulbar palsy.

In some patients however, there is a combination of clinical patterns.

**Amyotrophic lateral sclerosis (ALS):**

- The most common type of MND (**50% of patients**).
- Typically **LMN** signs in arms and **UMN** signs in legs.
- In familial cases the gene responsible lies on chromosome 21 and codes for superoxide dismutase.

**Primary lateral sclerosis:**

- **UMN** signs only.

**Progressive muscular atrophy:**

- **LMN** signs only.
- Affects distal muscles before proximal
- Carries **best prognosis**

### Progressive bulbar palsy:

- Palsy of the tongue, muscles of chewing/swallowing and facial muscles due to loss of function of brainstem motor nuclei.
- Carries **worst prognosis**.

## Diagnosis:

- **EMG** (Electromyography) shows a ↓ number of action potentials with a ↑ amplitude.
- **MRI** is usually performed to exclude the differential diagnosis of cervical cord compression and myelopathy.

## Management:

### Riluzole (Rilutek®):

- Prevents stimulation of glutamate receptors (Anti-glutamate).
- Used **mainly in amyotrophic lateral sclerosis.**
- Prolongs life by about 3 months.
- Expensive.

### Respiratory care:

- **NIV** (Non-invasive ventilation, usually BIPAP) is used at night.
- Studies have shown that **NIV has a survival benefit** of around 7 months.

**MND** (Motor neuron disease) >>> **ttt**: **NIV** is better than Riluzole.

## Prognosis

- **poor**: 50% of patients die within 3 years.

# Dystrophinopathies

## Overview

- **X-linked recessive**
- due to mutation in the gene encoding dystrophin, dystrophin gene on Xp21
- dystrophin is part of a large membrane associated protein in muscle which connects the muscle membrane to actin, part of the muscle cytoskeleton
- in Duchenne muscular dystrophy there is a frameshift mutation resulting in one or both of the binding sites are lost leading to a severe form
- in Becker muscular dystrophy there is a non-frameshift insertion in the dystrophin gene resulting in both binding sites being preserved leading to a milder form

## Duchenne muscular dystrophy

- progressive proximal muscle weakness **from 5 years**
- calf pseudohypertrophy
- Gower's sign: child uses arms to stand up from a squatted position
- 30% of patients have intellectual impairment

## Becker muscular dystrophy

- develops after the age of 10 years
- intellectual impairment much less common

# Neuromyelitis optica

Neuromyelitis optica (NMO) is a monophasic or relapsing-remitting demyelinating CNS disorder Although previously thought to be a variant of multiple sclerosis, it is now recognised to be a distinct disease, particularly prevalent in Asian populations.

It typically involves the optic nerves and cervical spine, with imaging of the brain frequently normal.

Vomiting is also a common presenting complaint.

**Diagnosis** requires bilateral optic neuritis, myelitis and 2 of the following 3 criteria:

- Spinal cord lesion involving 3 or more spinal levels
- Initially normal MRI brain
- **Aquaporin 4 positive serum antibody**

### Management

- immunosuppressant e.g. with anti-CD20 agent rituximab)

## Duchenne muscular dystrophy

- progressive proximal muscle weakness from 5 years
- calf pseudohypertrophy
- Gower's sign: child uses arms to stand up from a squatted position
- 30% of patients have intellectual impairment

## Becker muscular dystrophy

- develops after the age of 10 years
- intellectual impairment much less common

## Facioscapulohumeral muscular dystrophy

Facioscapulohumeral muscular dystrophy (FSHMD) is an autosomal dominant form of muscular dystrophy.
As the name suggests it typically affects the face, scapula and upper arms first. Symptoms typically present by the age of 20 years.

### Features

- facial muscles are involved first - difficulty closing eyes, smiling, blowing etc
- weakness of the shoulder and upper arm muscles
- abnormal prominence of the borders of the shoulder blades - 'winging'
- lower limb: hip girdle weakness, foot drop

# Epilepsy

**Classification**: Epilepsy: classification – refer to nice guideline April 2022

## Basics:

- Two main categories are **generalised** and **partial** seizures
- Partial seizures may progress to general seizures
- Other types: myoclonic, atypical absence, atonic and tonic seizures are usually seen in childhood

**Generalised** - no focal features, consciousness lost immediately:

- **Grand mal (tonic-clonic)**
- **Petit mal (absence seizures)** absences last a few seconds and are associated with a quick recovery, mostly seen in children
  - **1st line treatment ethosuximide**
  - good prognosis 90-95% become seizure free in adolescence
- **Myoclonic jerks**: brief, rapid muscle jerks
- Partial seizures progressing to generalised seizures
- Infantile spasms

**Partial** - focal features depending on location:

- Simple (**no disturbance** of consciousness or awareness)
- Complex (consciousness is disturbed)
- Simple partial followed by impaired consciousness, or consciousness impaired at onset
- Partial seizures with secondary generalisation
- Temporal lobe → aura, déjà vu, jamais vu; motor → Jacksonian

Consider lamotrigine or levetiracetam as first-line monotherapy for people with focal seizures (2022).

With simple partial seizures there is no disturbance of consciousness or awareness. Lip smacking is an example of an automatism- an automatic, repetitive act.

### Epilepsy: localizing features of focal seizures

| Location | Typical seizure type |
|---|---|
| Temporal lobe (HEAD) | Hallucinations (auditory/gustatory/olfactory), Epigastric rising/Emotional, Automatisms (lip smacking/grabbing/plucking), Deja vu/Dysphasia post-ictal) |
| Frontal lobe (motor) | Head/leg movements, posturing, post-ictal weakness, Jacksonian march |
| Parietal lobe (sensory) | Paraesthesia |
| Occipital lobe (visual) | Floaters/flashes |

## Investigation

- Electroencephalogram (EEG)
- Neuroimaging

## Treatment

Most neurologists now start antiepileptic drugs (**AED**) following a **second** epileptic seizure.

NICE guidelines suggest starting antiepileptic after the **first** seizure **if any** of the following are present: **(4):**

1) The patient has a **neurological** deficit.
2) **Brain imaging** shows a structural abnormality.
3) **EEG** shows unequivocal epileptic activity.
4) The patient or their family consider the risk of having a **further** seizure unacceptable.

**Monotherapy** should be attempted before combination therapy is started.

A study of patients with previously untreated epilepsy demonstrated that **47%** achieved control of seizures with the use of their **first single** drug.

**14%** became seizure-free during treatment with a **second or third drug.**

An additional **3%** became seizure-free with the use of **two drugs simultaneously.**

### Generalised tonic-clonic seizures:

- **Sodium valproate**
- Second line: **Lamotrigine** (Lamictal®) or levetiracetam.

### Absence seizures (Petit mal):

- sodium valproate or ethosuximide

- **Consider sodium valproate** as first-line treatment for absence seizures with other seizure types (or at risk of these) in:
  - boys and men
  - girls aged under 10 years and who are unlikely to need treatment when they are old enough to have children
  - women who are unable to have children.
- **Consider lamotrigine or levetiracetam** as second line option or first-line treatment options in women and girls able to have children (including young girls who are likely to need treatment when they are old enough to have children) with absence seizures and other seizure types (or at risk of these).

If the first choice is unsuccessful, consider the other of these options.

**Myoclonic seizures:**

- **Sodium valproate**
- if sodium valproate is unsuccessful as first-line treatment for myoclonic seizures, offer **levetiracetam** as a second-line monotherapy or add-on treatment.

**Partial seizures:**

- **lamotrigine or levetiracetam as first-line monotherapy for people with focal seizures (2022).**

**Indications for monitoring of AED blood levels**

- detection of non-adherence to the prescribed medication
- suspected toxicity
- adjustment of phenytoin dose
- management of pharmacokinetic interactions (for example, changes in bioavailability, changes in elimination, and co-medication with interacting drugs)
- specific clinical conditions, for example, status epilepticus, organ failure and certain situations in pregnancy

**Stopping of anti-epileptic drugs (AED)**

- **Can be considered if seizure free for at least 2 years, with AEDs being stopped slowly over 2-3 months** (withdrawing benzodiazepines and barbiturates may take up to 6 months or longer)
- Benzodiazepines should be withdrawn over a longer period.

**Vagus nerve stimulation**

- indicated for use as an adjunctive therapy in reducing the frequency of seizures in adults who are refractory to antiepileptic medication

If there are absence or myoclonic seizures, or if juvenile myoclonic epilepsy (JME) iss suspected, do not offer carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine or vigabatrin.

AED cessation can be considered if seizure free for> 2 years Stop AEDs over 2-3 months

## Absence seizures (petit mal)-details

It is a form of generalised epilepsy that is mostly seen in children.
The typical age of onset of **3-10 years old** and **girls** are affected twice as commonly as boys.

### Features:

- Absences last a **few seconds** and are associated with **a quick recovery**.
- Seizures may be provoked by **hyperventilation** or **stress**.
- The child is usually **unaware** of the seizure.
- They may occur **many times a day**.
- EEG: bilateral, symmetrical 3Hz spike and wave pattern.

### Management:

**Offer ethosuximide as first-line treatment for absence seizures.**

**If first-line treatment** is unsuccessful, offer sodium valproate as second-line monotherapy or add-on treatment for absence seizures in:

- boys of all ages
- girls aged under 10 years and who are unlikely to need treatment when they are old enough to have children
- women who are unable to have children.

**N.B**: Carbamazepine may actually exacerbate absence seizure.

**NB**: **Gelastic seizures** should be suspected in cases of **erratic laughing** or **crying**. It can be hard to identify **in young children** but there is usually associated automatisms such as fidgeting or lip smacking or change in sensorium.

## Myoclonic epilepsy-details

**Juvenile myoclonic epilepsy** is the **commonest** of the **idiopathic** generalised epilepsies.

**Typically,** first manifests itself **between the ages of 10 and 20** with brief episodes of involuntary muscle twitching occurring early in the morning.

**Precipitating factors** include alcohol, menstruation and sleep deprivation. The condition is genetically linked to the **short arm of chromosome 6**.

### Investigations

- **Interictal EEG is diagnostic showing,** generalised spike- and polyspike-wave activity; a photosensitive response may also be present

### Management

**Female of childbearing potential**

- lamotrigine, levetiracetam or topiramate
- **2nd line:** add lamotrigine levetiracetam, or topiramate

**Male or female who are not of childbearing potential**

- **sodium valproate**
- **2nd line:** add lamotrigine levetiracetam, or topiramate
- responds extremely well to sodium valproate
- other options include, lamotrigine and topiramate.

**Prognosis** is extremely favourable if the condition is treated correctly, with many patients becoming seizure-free.

## Status epilepticus

Status epilepticus is defined as:

- a single seizure lasting >5 minutes, or
- >= 2 seizures within a 5-minute period without the person returning to normal between them

This is a medical emergency. The priority is the termination of seizure activity, which if prolonged will lead to irreversible brain damage.

### Management

- ABC
  - airway adjunct
  - oxygen
  - check blood glucose
- First-line drugs are IV benzodiazepines such as diazepam or lorazepam
  - in the prehospital setting PR diazepam or buccal midazolam may be given
  - in hospital **IV lorazepam** is generally used. This may be repeated once after 10-20 minutes
- If ongoing (or 'established') status it is appropriate to start a second-line agent such as **phenytoin or phenobarbital infusion**
- If no response ('refractory status') within 45 minutes from onset, then the best way to achieve rapid control of seizure activity is induction of general anaesthesia.

## Benign rolandic epilepsy

Benign rolandic epilepsy is a form of childhood epilepsy that typically occurs between the age of 4 and 12 years.

### Features

- seizures characteristically occur at night
- seizures are typically partial (e.g. paraesthesia affecting face) but secondary generalisation may occur (i.e. parents may only report tonic-clonic movements)
- child is otherwise normal

**EEG** characteristically shows centro-temporal spikes

**Prognosis** is excellent, with seizures stopping by adolescence

## Epilepsy: pregnancy and breast feeding

The risks of uncontrolled epilepsy during pregnancy generally outweigh the risks of medication to the foetus, so **her drug should be continued**.

There is **no point in switching therapies** as this could **precipitate** seizures in an otherwise stable patient.

All women thinking about becoming pregnant should be advised to take **folic acid 5 mg per day well before pregnancy** to **minimise** the **risk** of **neural tube defects.**

Around 1-2% of new born to non-epileptic mothers have congenital defects. This rises to 3-4% if the mother takes antiepileptic medication.

## Other points:

Consider more frequent monitoring reviews for women and girls with epilepsy

**who are pregnant and are prescribed antiseizure medication, if they:**

- have a learning disability
- are aged under 16 years

**Epilepsies in children, young people and adults .**

- have active epilepsy (a seizure within the past 12 months)
- have bilateral tonic-clonic seizures
- have modifiable risk factors for SUDEP (sudden unexpected death in epilepsy).

**Be aware that potentially modifiable risk factors for SUDEP include:**

- non-adherence to medication
- alcohol and drug misuse
- having focal to bilateral tonic-clonic seizures or generalised tonic-clonic seizures
- having uncontrolled seizures
- living alone
- sleeping alone without supervision.
- Aim for **monotherapy**.
- There is **no** indication to **monitor** antiepileptic drug (AED) levels.
- Phenytoin: associated with cleft palate.
- Sodium valproate: associated with neural tube defects.
- Similarly, both phenytoin and valproate are associated with teratogenic effects.
- **Levetiracetam and lamotrigine can be used in pregnancy.**
- Topiramate: is associated with major congenital malformation (MCM).
- **Carbamazepine**: often considered the **least** teratogenic of the older antiepileptic.
- In pregnancy total plasma concentrations of anticonvulsants fall, so the **dose** of Carbamazepine **may** need to be **increased**.

- The potential teratogenic effects (particularly **neural tube defects)** of **carbamazepine** do need to be **explained** and in an effort to reduce this risk she should receive **folate** supplements.
- **Screening with alpha fetoprotein (AFP)** and **2nd trimester ultrasound** are required.
- **Lamotrigine**:The dose of lamotrigine may need to be increased in pregnancy.
- Lowest rate of MCM were seen for **Carbamazepine** and **Lamotrigine**.
- **Vitamin K** should be given to the mother **prior to delivery**.

The Medicines and Healthcare products Regulatory Agency (MHRA) has announced ( on April 2018) that valproate medicines – used to treat epilepsy and bipolar disorder – must no longer be prescribed to women of child bearing age unless she is on a pregnancy prevention programme (PPP).

The BNF states **'breast-feeding** is acceptable and generally considered **safe** for mothers with **all antiepileptic drugs**, taken in normal doses, with the possible exception of barbiturates'.
**Breast feeding is acceptable with nearly all anti-epileptic drugs.**

## Narcolepsy

### Overview

- associated with HLA-DR2
- it is associated with **low levels of orexin (hypocretin),** a protein which is responsible for controlling appetite and sleep patterns
- early onset of REM sleep

### Features

- typical onset in teenage years
- hypersomnolence
- cataplexy (sudden loss of muscle tone often triggered by emotion)
- sleep paralysis
- vivid hallucinations on going to sleep or waking up

### Investigation

- multiple sleep latency EEG

### Management

- daytime stimulants (e.g. **modafinil**) and nighttime sodium oxybate

## Cataplexy

Cataplexy describes the **sudden** and **transient loss of muscular tone** caused by **strong emotion** (e.g. laughter, being frightened).
**Around** two-thirds of patients with narcolepsy have cataplexy.
**Features** range from buckling knees to collapse.

## Pseudoseizures

### Overview

- Pseudoseizures are commonly misdiagnosed as true seizures and treated inappropriately with anti-epileptic drugs.
- patients of any age can present with pseudoseizures
- features such as tongue biting and urinary incontinence are not absolute features of an organic seizure, they are often present in pseudoseizures.

### Factors favoring pseudoseizures

- pelvic thrusting
- family member with epilepsy
- accompanying underlying psychiatric concerns, e.g. **crying after seizure**, tearful around the time of the seizure.
- more common in females
- attacks in public and absence of nocturnal events (don't occur when alone)
- gradual onset
- **prolonged nature of the attacks (15-30 minutes)**
- Violent shaking,
- **resistance to passive eye opening**
- **very short post-ictata**
- normal vital signs

**Urinary incontinence can also occur in pseudoseizures, but tongue biting is rare.**

### Factors favoring true epileptic seizures

- tongue biting
- raised serum prolactin

**Diagnosis: Video telemetry is useful for differentiating**
**Treatment:** Simple **observation** is the appropriate management.

# Huntington's disease

Huntington's disease is an inherited neurodegenerative condition. It is a progressive and incurable condition that typically results in death 20 years after the initial symptoms develop.

## Genetics

- **autosomal dominant**
- **trinucleotide repeat disorder: repeat expansion of CAG**
  - as Huntington's disease is a trinucleotide repeat disorder, the phenomenon of anticipation may be seen, where the disease is presents at an earlier age in successive generations
- results in degeneration of cholinergic and GABAergic neurons in the striatum of the basal ganglia
- due to defect in huntingtin gene on chromosome 4

**Features** typical develop after 35 years of age

- chorea
- personality changes (e.g. irritability, apathy, depression) and intellectual impairment
- dystonia
- saccadic eye movements

# Headaches

Headaches: please refer to nice guidelines on management of headaches updated in 2021

### Tension-type headache, migraine and cluster headache

- Diagnose tension-type headache, migraine or cluster headache according to the headache features in the table. **Remember that chronic migraine and chronic tension-type headache commonly overlap. If there are any features of migraine, diagnose chronic migraine.**

Woman with daily tension-type headache. This is a primary headache.

## Acute treatment:

- Consider aspirin, paracetamol or an NSAID for the acute treatment of tension-type headache, taking into account the person's preference, comorbidities and risk of adverse events. Because of the association with Reye's syndrome, preparations containing aspirin should not be offered to under 16s. Do not offer opioids for the acute treatment of tension-type headache.

## Prophylactic treatment:

- Consider a course of up to 10 sessions of acupuncture over 5 to 8 weeks for the prophylactic treatment of chronic tension-type headache

# Medication overuse headache

Be alert to the possibility of medication overuse headache in people whose headache developed or worsened while they were taking the following drugs for 3 months or more:

- triptans, opioids, ergots or combination analgesic medications on 10 days per month or more or
- paracetamol, aspirin or an NSAID, either alone or any combination, on 15 days per month or more.

## Management

- Advise people to stop taking all overused acute headache medications for at least 1 month and to stop abruptly rather than gradually.
- Advise people that headache symptoms are likely to get worse in the short term before they improve and that there may be associated withdrawal symptoms, and provide them with close follow-up and support according to their needs.
- Consider prophylactic treatment for the underlying primary headache disorder in addition to withdrawal of overused medication for people with medication overuse headache
- Consider specialist referral and/or inpatient withdrawal of overused medication for people who are using strong opioids, or have relevant comorbidities, or in whom previous repeated attempts at withdrawal of overused medication have been unsuccessful.
- Review the diagnosis of medication overuse headache and further management 4 to 8 weeks after the start of withdrawal of overused medication.
- opioid analgesics should be gradually withdrawn

The differential diagnoses in a patient presenting with **headaches** and **painful diplopia** are:

1) A posterior communicating aneurysm (PCA).
2) Ophthalmoplegic migraine.
3) Pituitary adenoma/ Apoplexy.
4) Cavernous sinus thrombosis, or
5) A medical mononeuritis.

**Conventional angiography** is the definitive procedure for the detection and characterisation of cerebral aneurysms.
**Digital subtraction angiography** may be helpful in identifying an acutely ruptured aneurysm.

# Headache

Headache accounts for a large proportion of medical consultations. The table below summarizes the main characteristics of common or important causes:

| Condition | Notes |
|---|---|
| **Migraine** | Recurrent, severe headache which is usually unilateral and throbbing in nature<br>May be associated with aura, nausea and photosensitivity<br>Aggravated by, or causes avoidance of, routine activities of daily living. Patients often describe 'going to bed'.<br>In women may be associated with menstruation |
| **Tension headache** | Recurrent, non-disabling, bilateral headache, often described as a 'tight-band'<br>Not aggravated by routine activities of daily living |
| **Cluster headache*** | Pain typical occurs once or twice a day, each episode lasting 15 mins - 2 hours with clusters typically lasting 4-12 weeks<br>Intense pain around one eye (recurrent attacks 'always' affect same side)<br>Patient is restless during an attack<br>Accompanied by redness, lacrimation, lid swelling<br>More common in men and smokers |
| **Temporal arteritis** | Typically patient > 60 years old<br>Usually rapid onset (e.g. < 1 month) of unilateral headache<br>Jaw claudication (65%)<br>Tender, palpable temporal artery<br>Raised ESR |
| **Medication overuse headache** | Present for 15 days or more per month<br>Developed or worsened whilst taking regular symptomatic medication<br>Patients using opioids and triptans are at most risk<br>May be psychiatric co-morbidity |

### Other causes of headache

#### Acute single episode

- meningitis
- encephalitis
- **subarachnoid haemorrhage**
- head injury
- **sinusitis**
- **glaucoma (acute closed-angle)**
- tropical illness e.g., Malaria

#### Chronic headache

- **chronically raised ICP**
- Paget's disease
- psychological

## Migraine-details

**Migraine is a common type of primary headache. It is characterised typically by:**

- a severe, unilateral, throbbing headache
- associated with nausea, photophobia and phonophobia
- attacks may last up to 72 hours
- patients characteristically go to a darkened, quiet room during an attack
- 'classic' migraine attacks are precipitated by an aura. These occur in around one-third of migraine patients
- typical aura are visual, progressive, last 5-60 minutes and are characterised by transient hemianopic disturbance or a spreading scintillating scotoma
- formal diagnostic criteria are produced by the International Headache Society (see below)

### Epidemiology

- 3 times more common in women
- prevalence in men is around 6%, in women 18%

### Common triggers for a migraine attack

- tiredness, stress
- alcohol
- combined oral contraceptive pill
- lack of food or dehydration

- cheese, chocolate, red wines, citrus fruits
- menstruation
- bright lights

## Diagnostic criteria

The International Headache Society has produced the following diagnostic criteria for migraine without aura.

| Point | Criteria |
|---|---|
| A | At least 5 attacks fulfilling criteria B-D |
| B | Headache attacks lasting **4-72 hours*** (untreated or unsuccessfully treated) |
| C | **Headache has at least two of the following characteristics:**<br>**1) unilateral location***<br>**2) pulsating quality (i.e., varying with the heartbeat)**<br>**3) moderate or severe pain intensity**<br>**4) aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs)** |
| D | During headache at least one of the following:<br>**1) nausea and/or vomiting***<br>**2) photophobia and phonophobia** |
| E | Not attributed to another disorder (history and examination do not suggest a secondary headache disorder or, if they do, it is ruled out by appropriate investigations or headache attacks do not occur for the first time in close temporal relation to the other disorder) |

*In children, attacks may be shorter-lasting, headache is more commonly bilateral, and gastrointestinal disturbance is more prominent.

### Migraine with aura

**N.B: Migraine with aura (around around 25% of migraine patients)** tends to be easier to diagnose with a typical aura being progressive in nature and may occur hours prior to the headache. Typical aura includes a transient hemianopic disturbance or a spreading scintillating scotoma ('jagged crescent'). Sensory symptoms may also occur.

**NB: A complicated migraine** is one which results in **hemi** sensory or **hemi** motor findings associated with a typical migraine presentation i.e., **it is like TIA but** the patient is **young** age and has **past medical history for migraines**.

If we compare these guidelines to the **NICE criteria** the following points are noted:

NICE suggests migraines may be unilateral or bilateral

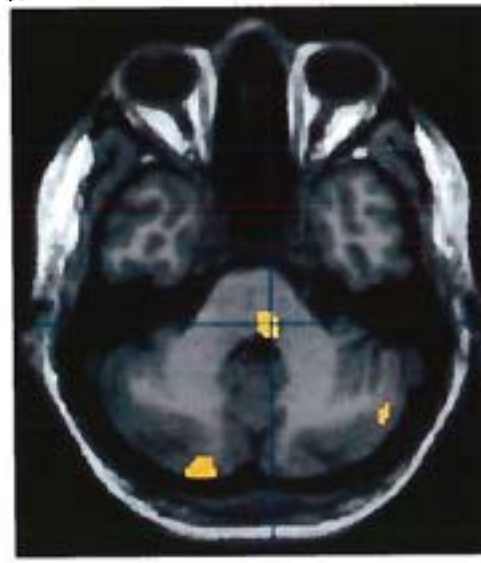
NICE also give more detail about typical auras:

**Auras may occur with or without headache and:**

- are fully reversible
- develop over at least 5 minutes
- last 5-60 minutes

The following aura symptoms are atypical and may prompt further investigation/referral;

- motor weakness
- double vision
- visual symptoms affecting only one eye
- poor balance
- decreased level of consciousness.



Imaging has helped clarify the etiology of migraine disorder. This positron emission tomography image shows activation in the dorsolateral pons, which includes the noradrenergic locus coeruleus, an area that modulates nociceptive input from the meningeal vessels.

## Management

It should be noted that as a general rule **5-HT receptor agonists** are used in the acute treatment of migraine whilst **5-HT receptor antagonists** are used in prophylaxis.

**AC**ute → 5HT1 **Ag**onist(triptans)
Prophylaxis → 5HT2 antagonist & βB

**Migraine:**
- **Acute**: (Triptan + NSAID) **or** (Triptan + paracetamol).
- **Prophylaxis**: Topiramate (Topamax®) or propranolol.

## Acute treatment:

- First-line: offer combination therapy with an **oral triptan** and an **NSAID**, or an oral triptan and paracetamol.
- For young people aged 12-17 years consider a **nasal triptan** in preference to an oral triptan.
- If the above measures are not effective or not tolerated offer a non-oral preparation of metoclopramide or prochlorperazine and consider adding a non-oral NSAID or triptan

### Prophylaxis:

- Prophylaxis should be given **if** patients are **experiencing ≥ 2 attacks per month**. Modern treatment is effective in about 60% of patients.
- NICE advice either **Topiramate (Topamax®)** or **Propranolol 80 – 240 mg OD** according to the person's preference, comorbidities and risk of adverse events'.
- Propranolol should be used in preference to topiramate in women of child bearing age as it may be teratogenic and it can reduce the effectiveness of hormonal contraceptives.
- If these measures fail NICE recommend 'a course of up to 10 sessions of **acupuncture** over 5-8 weeks' or **gabapentin**.
- NICE recommend: 'Advise people with migraine that **riboflavin** (400 mg once a day) may be effective in reducing migraine frequency and intensity for some people'
- For women with predictable menstrual migraine treatment NICE recommend either frovatriptan (2.5 mg twice a day) or zolmitriptan (2.5 mg twice or three times a day) as a type of 'mini-prophylaxis'.
- Review the need for continuing migraine prophylaxis 6 months after the start of prophylactic treatment
- **5-HT2 antagonists** like:
  - "**Pizotifen**" is no longer recommend. Adverse effects such as weight gain & drowsiness are common.
  - "**Methysergide**" is very **rarely** used as associated with retroperitoneal fibrosis.

**Avoid aspirin** in children **< 16 years** as risk of Reye's syndrome

**Codeine** would also be a **poor** choice as it has **limited benefit in migraine.**

Patients with **migraine** experience **delayed gastric emptying** during **acute attacks**. So, **decrease effect of analgesics**. For this reason, analgesics are often combined **prokinetic** agents such as metoclopramide.

### Topiramate side effects:

- **Renal stones**
- **Weight loss**
- **Cognitive impairment**
- **Tingling** in extremities.

## Migraine: pregnancy, contraception and other hormonal factors

### Migraine during pregnancy:

- **Paracetamol** 1g is first-line
- **Aspirin** 300mg or **ibuprofen** 400mg can be used second-line in the first and second trimester.

### Migraine and menstruation:

**Suspect menstrual-related migraine in women and girls whose migraine occurs predominantly between 2 days before and 3 days after the start of menstruation in at least 2 out of 3 consecutive menstrual cycles.**

- SIGN recommends that women are treated with **mefenamic acid** or a combination of **aspirin**, **paracetamol** and **caffeine**.
- **Triptans** are also recommended in the acute situation, NICE recommend either frovatriptan (2.5 mg twice a day) or zolmitriptan (2.5 mg twice or three times a day) as a type of 'mini-prophylaxis'.

### Migraine and the combined oral contraceptive (COC) pill:

- If patients have migraine with aura, then the COC is **absolutely contraindicated** due to an **increased risk of stroke**
- Ergot derived compounds and triptans are contraindicated for the treatment of **hemiplegic migraine** because of the risk of precipitating a stroke.

### Migraine and hormone replacement therapy (HRT):

- Safe to prescribe HRT for patients with a history of migraine but it may make migraines **worse**.

**Evaluate people who present with headache and any of the following features, and consider the need for further investigations and/or referral:**

- worsening headache with fever.
- sudden-onset headache reaching maximum intensity within 5 minutes.
- new-onset neurological deficit.
- new-onset cognitive dysfunction.
- change in personality.
- impaired level of consciousness
- recent (typically within the past 3 months) head trauma.
- headache triggered by cough, valsalva (trying to breathe out with nose and mouth blocked) or sneeze.
- headache triggered by exercise.
- orthostatic headache (headache that changes with posture).
- symptoms suggestive of giant cell arteritis.
- symptoms and signs of acute narrow angle glaucoma.

**Consider further investigations and/or referral for people who present with new-onset headache and any of the following:** • compromised immunity, caused, for example, by HIV or immunosuppressive drugs • age under 20 years and a history of malignancy • a history of malignancy known to metastasize to the brain • vomiting without other obvious cause.

## Cluster headache (CH)

Cluster headaches are more common in **men** (10:1) and **smokers**.
More common in younger males below the age of 40

### Features:

- Pain typical occurs **once or twice a day**, **each episode lasting 15 mins - 2 hours.**
- Clusters typically last 4-12 weeks.
- **Intense pain around one eye** (**recurrent** attacks **'always'** affect **same** side).
- Accompanied by **eye redness, lacrimation, lid swelling**
- **Miosis** and **ptosis** in a minority.
- **Nasal** stuffiness, **Rhinorrhoea.**
- Patient is **restless during an attack**
- Examination between the attacks should be normal.

Episodic eye pain, lacrimation, nasal stuffiness occurring daily >>> cluster headache

Lacrimation, ptosis, and lid edema seen in cluster headache.

**Management:**

- **Acute**: **use 100% oxygen at a flow rate of at least 12 litres per minute with a non-rebreathing mask and a reservoir bag and, SC or nasal Sumatriptan** and nasal lidocaine.
- **Prophylaxis**: **Verapamil**, prednisolone.
- Consider specialist referral
  N.B: Some neurologists use the term trigeminal autonomic cephalgia to group a number of conditions including cluster headache (CH), chronic paroxysmal hemicrania (CPH) and short-lived unilateral neuralgiform headache with conjunctival injection and tearing (SUNCT).
- NICE recommend seeking specialist advice from a neurologist if a patient develops cluster headaches with respect to neuroimaging

**NB**: **Sumatriptan** has been associated with **chest pain** in up to 17% of cases, possibly due to **vasospasm**. Also it is associated with **MI** and so **contraindicated** in people with known **IHD**.

**D.D: Chronic paroxysmal hemicrania (CPH)** has features of cluster headaches but is associated with attacks of **shorter duration** and **increased frequency** e.g., each headache can last between **3-45 minutes** and occur **20-40 times per day**. It responds very well to **indomethacin**.

Sudden onset of a thunderclap headache prompted imaging that showed diffuse subarachnoid hemorrhage with associated ventricular hemorrhage. Top arrow indicates blood in interhemispheric fissure. Bottom arrow indicates blood in lateral ventricle.

## Pituitary apoplexy

**Sudden** enlargement of pituitary tumour **secondary** to haemorrhage or infarction. A pituitary adenoma usually pre-exists.

Endocrinologically, the main initial problem is a **lack of adrenocorticotropic hormone (ACTH),** which results in a lack of cortisol and the features of an **'Addisonian crisis'**, i.e. hypotension, hyponatraemia, hyperkalaemia and hypoglycaemia. Subacutely, there can be deficiency in thyroid stimulating hormone (TSH) and gonadotropins (LH and FSH).

### Precipitating factors

- hypertension
- pregnancy
- trauma
- anticoagulation

### Features:

- **Sudden onset headache** similar to that seen in SAH.
- **Vomiting**
- **Neck stiffness**
- **Visual field defects**: classically **bitemporal superior** quadrantic defect.
- **Extra ocular** nerve palsies in up to 80%, with **III** nerve palsy the commonest finding.
- Features of pituitary insufficiency e.g. **Hypotension** secondary to **hypoadrenalism**.

### Investigation

- **MRT pituitary** to confirm the diagnosis.

### Management

- urgent steroid replacement due to loss of ACTH
- careful fluid balance
- surgery

**EX:** A 47-year-old man presents to the Emergency Department with a 3 day history of severe headache associated with vomiting. There is no past medical history of

. **On examination** blood pressure is 98/62 mmHg, pulse is 108 bpm and temperature is 37.0°C. There is mild neck stiffness and a partial third nerve palsy of the left eye. Blood rests reveal: $Na^+$ = 130, K= 5.2, Low free T4. The most likely diagnosis is >> Pituitary apoplexy..

## Post-lumbar puncture headache

Headache following lumbar puncture (LP) occurs in approximately **one-third** of patients. The pathophysiology of is unclear but may relate to a 'leak' of CSF following dural puncture.

It is more common in **young females** with a low body mass index.

### Typical features:

- Usually develops **within 24-48 hours following LP** but may occur **up to one week later.**
- **May last several days.**
- **Worsens with upright position.**
- **Improves with recumbent position.**

| Factors which may contribute to ↑↑↑headache | Factors which do not contribute to headache |
|---|---|
| • Increased needle size<br>• Direction of bevel<br>• Not replacing the stylet<br>• Increased number of LP attempts<br>• **Use of a Quincke (sharp) needle** | • Increased volume of CSF removed<br>• Bed rest following procedure<br>• Increased fluid intake post procedure<br>• Opening pressure of CSF<br>• Position of patient |

### Management:

- **Supportive** initially (analgesia, rest).
- If pain continues for more than 72 hours then specific treatment is indicated, to prevent subdural haematoma.
- **TTT** options include: **blood patch**, epidural saline and caffeine I.V.

**What is the most appropriate type of needle to use in lumbar puncture?**

- **20G Sprotte® (atraumatic) needle**
- Studies show that smaller atraumatic needles reduce the risk of post-lumbar puncture headache.

## Idiopathic intracranial hypertension (IIH)

Idiopathic intracranial hypertension (also known as **pseudo tumour cerebri** and formerly **Benign Intracranial Hypertension (BIH)**) is a condition classically seen in **young, overweight females**.

Its exact cause is **unknown**, but it is most common in overweight young women.

IIH is thought to be due to **impaired CSF absorption** across the arachnoid villi into the dural sinuses.

It is characterised by **raised intracranial pressure** with **normal** CSF cell count and protein content, normal ventricular size, anatomy and position.

**If left untreated** it can result in **permanent visual loss.**

The symptoms classically reported with raised intracranial pressure are frontal headaches, worst when lying flat, coughing, bending, and on waking as well as nausea and vomiting. Patients may also complain of a whooshing sound in their ears, and pain/ numbness or tingling in their arms and legs. Visual symptoms include transient, bilateral episodes of blurred vision, transient visual field defects and double vision.

## Features:

- **Headache**
- **Blurred vision**
- **Fundus: Papilledema** with **reduced/absent retinal venous pulsation**
- **Enlarged blind spot**
- **Sudden loss of vision** (If the optic nerve becomes compressed).
- **6th nerve palsy** may be present >> **diplopia**
- Reflexes are **preserved** and **plantars are flexor**. Extensor plantars suggest an alternative diagnosis.
- **Normal** ventricles on CT and MRI
- **CSF opening pressure:** mild increase (more than 20 CmH2O).

Obese, young female with headaches, blurred vision and Papilledema, ± OCP (Dianette in PCO) but otherwise normal neurology >>> think idiopathic intracranial hypertension (IIH)

## Risk factors:

- **Obesity**
- **Female** sex
- Pregnancy
- **Drugs:**
  - **combined oral contraceptive pill**
  - **Steroids,**
  - **Tetracycline (Doxycycline for acne),**
  - **Vitamin A toxicity**
  - **Lithium**

## Management:

- **Weight loss.**
- Diuretics e.g., **acetazolamide**
- **topiramate is also used, and has the added benefit of causing weight loss in most patients**
- **Repeated lumbar puncture or Lumbo-peritoneal (LP) shunt.**
- Surgery: **optic nerve sheath decompression and fenestration** may be needed to prevent damage to the optic nerve
- . A lumboperitoneal or ventriculoperitoneal shunt may also be performed to reduce intracranial pressure

**NB: Visual loss** is the single threatening complication of idiopathic intracranial hypertension (IIH).

**NB:** If intracranial hypertension is thought to occur secondary to a known **causes** (e.g. Medication) then it is of course not idiopathic.

**EX:** A 27-year-old woman is reviewed due to sudden loss of vision in her left eye. She is known to have severe RA and is treated currently with methotrexate, infliximab and prednisolone. She has in the past also used sulfasalazine and hydroxychloroquine. For the past 6 weeks she has developed troublesome headaches. Examination demonstrates **bilateral papilledema**. Which one of the following is most likely to be responsible for this presentation? >> **Intracranial hypertension** probably **secondary to prednisolone**. Patients may lose sight suddenly if the optic nerve becomes compressed.

## Neurofibromatosis (NF)

There are two types of neurofibromatosis, NF1 and NF2.

Both are inherited in an **autosomal dominant** fashion.

NF1 is also known as von Recklinghausen's syndrome. It is caused by a gene mutation on **chromosome 17** which encodes neurofibromin and affects around 1 in 4,000.

NF2 is caused by gene mutation on **chromosome 22** and affects around 1 in 100,000.

### Features:

| NF1 | NF2 |
|---|---|
| • **Café-au-lait spots** (>= 6 to 15 mm in diameter)<br>• **Axillary/groin freckles**<br>• **Iris: Lisch nodules** in **> 90%**<br>• **Optic glioma**<br>• **Scoliosis**<br>• **Pheochromocytomas**<br>• Peripheral neurofibromas<br>• A family history in only 50% | • **Bilateral vestibular schwannomas (acoustic neuromas)** → affecting the vestibulocochlear nerve → tinnitus, hearing loss, or vertigo<br>• **Early-onset cataracts**, usually bilateral<br>• Multiple cerebral and spinal tumors (especially meningiomas and ependymomas) |

## Diagnosis

- MRI of the brain and spine with contrast
- Ophthalmological exam
- Auditory testing
- Genetic testing

## Treatment

- Excision or resection of tumors (e.g., meningiomas)
- Surgery for kyphoscoliosis in NF type 1
- Drugs targeting the mTOR pathway (e.g., sirolimus) to reduce tumor growth

- **NF1**: chromosome **17** - as neurofibromatosis has 17 characters.
- **NF2**: chromosome **22** - all the 2's
- **Lisch nodules** in **iris** are seen in **more than 90%.**

## Patients with neurofibromatosis may develop hypertension for 3 main reasons:

- **Coexistent essential hypertension**
- **Renal vascular stenosis** secondary to fibromuscular dysplasia
- **Pheochromocytomas**

A 44-year-old Hispanic man with neurofibromatosis type 1 showing all the typical findings including neurofibromas, café-aulait spots, and axillary freckling.

Close-up of axillary freckling (Crow sign) with large café-au-lait spot on arm.

Close-up of neurofibromas on the back of the man .These are soft and round

A man with neurofibromatosis covered with neurofibromas.

Plexiform neurofibroma on the thenar eminence feels like a bag of worms in this man with neurofibromatosis. It is a benign tumor of the peripheral nerve sheath and is most often asymptomatic.

Lisch nodules (melanotic hamartomas of the iris) are clear yellow-to-brown, dome-shaped elevations that project from the
surface of this blue iris. These hamartomas are the most common type of ocular involvement in neurofibromatosis type 1 and do not affect vision.

Neurofibromas on the lower lid with Lisch nodules (dark brown spots) on the iris of this 64-year-old man with neurofibromatosis type 1.

Neurofibromatosis in a 62-year-old black woman. Note how large some the neurofibromas can become

**EX:** Pt. with **HTN** and has **large cafe-au-lait spots on his trunk and some axillary freckling** (i.e. **neurofibromatosis**), so you should:

- Check **renal function** to check diagnosis of renal vascular disease.
- Check **24 hr. urinary collection of catecholamines** to check Pheochromocytomas.

## Tuberous sclerosis (TS)

It is a genetic condition of **autosomal dominant** inheritance.

The responsible defects having been identified on both **chromosome 9 & 16**.

These chromosomes carry codes for hamartin and tuberin, protein gene products which are responsible for regulation of cell growth.

Like neurofibromatosis, the majority of features seen in TS are **neuro-cutaneous.**

### Cutaneous features:

- **Depigmented 'ash-leaf' spots** which fluoresce under UV light.
- **Shagreen patches**: roughened patches of skin over lumbar spine.
- **Adenoma sebaceum**: **butterfly distribution over nose.**
- **Fibromata beneath nails** (**subungual fibromata**).
- **Café-au-lait spots** may be seen (of course are more commonly associated with neurofibromatosis).

### Neurological features:

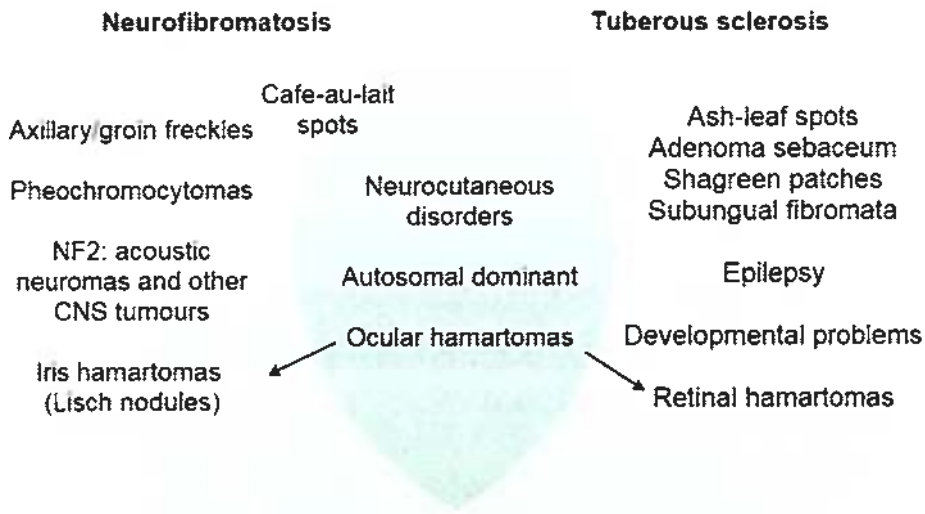
- **Developmental delay**
- **Intellectual impairment**
- **Epilepsy** (infantile spasms or partial)

### Also:

- **Retinal hamartomas**: dense white areas on retina (phakomata)
- Rhabdomyomas of the heart
- Gliomatous changes can occur in the brain lesions
- **Polycystic** kidneys, **renal angiomyolipomata, multiple lung cysts**

Angiofibromas (previously called adenoma sebaceum) on the face of a patient with tuberous sclerosis. The patient wasoriginally thought to have neurofibromatosis. He also has epilepsy and cognitive impairment, which accompanies tuberous sclerosis

**Cigarettes and coffee with a rough stupid person with a butterfly on his nose while he is dancing.**
Cigarettes (ash) – coffee (Café-au-lait spots) – stupid (Developmental and Intellectual) – dancing (epilepsy).



**MRCPUUK part 1 exam:** Generalised seizure + patches of hypopigmented skin + fibromata under finger nails. What is the most likely diagnosis?
**>> Tuberous sclerosis**

**MRCPUK part 1 exam:** H/O hypovolacmic shock. CT abdomen reveals a haemorrhagie lesion in the right kidney. biopsy shown it to be an angiomyolipomata. What is the most likely underlyine diagnosis?
**>> Tuberous sclerosis**

## Ataxic telangiectasia

### Basics:

- **Autosomal recessive** disorder
- Combined immunodeficiency disorder
- It typical presents in early childhood with abnormal movements. oculomotor apraxia and choreoathetosis developing later.

### Features:

- **Cerebellar ataxia**
- **Telangiectasia**
- **IgA deficiency resulting in recurrent chest infections**
- 10% risk of developing **malignancy**, lymphoma or leukaemia, but also non-lymphoid tumours

### Diagnosis

- Elevated **serum alpha-fetoprotein**, at least two standard deviations above the normal range, is diagnostic of ataxia-telangiectasia
- confirmed by the identification of mutations on the ATM gene.

### Prognosis

- Death in the late teens or 3rd decade from **bronchiectasis** is typical.

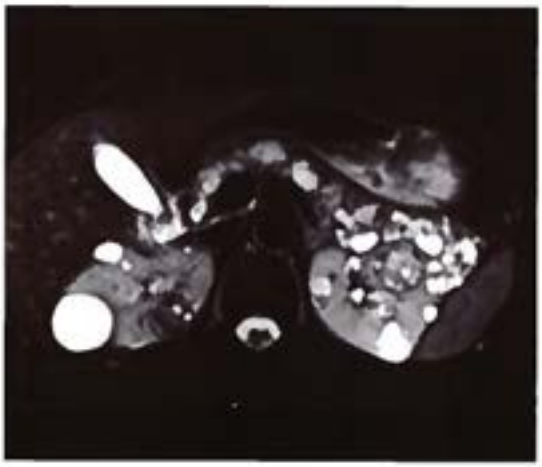
## Von Hippel-Lindau syndrome (VHL)

VHL syndrome is an **autosomal dominant** condition predisposing to **neoplasia**.

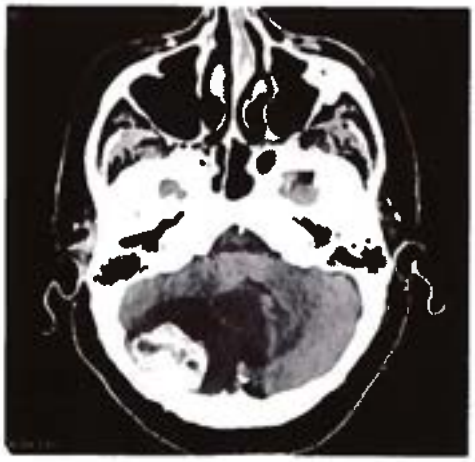
It is due to an **abnormality in the VHL gene** on **short arm of chromosome 3.**

## Features

- Cerebellar haemangiomas (**Ataxia**).
- Retinal haemangiomas: are bilateral in 25% of patients and may lead to **vitreous haemorrhage.**
- Renal cysts (premalignant).
- **Extra-renal cysts**: epididymis, pancreatic, hepatic.
- Phaeochromocytoma.
- Endolymphatic sac tumours.
- clear-cell renal cell carcinoma



MRI showing renal cysts in patient with known Von Hippel-Lindau syndrome.



CT scan showing a cerebellar hemangioma in a patient with Von Hippel-Lindau syndrome

## Cerebellar syndrome

Unilateral cerebellar lesions cause ipsilateral signs.

**Useful and well-known mnemonic to remember symptoms of cerebellar disease is DANISH:**

- **D** - Dysdiadochokinesia, Dysmetria (past-pointing), patients may appear 'Drunk'
- **A** - Ataxia (limb, truncal)
- **N** - Nystamus (horizontal = ipsilateral hemisphere)
- **I** - Intention tremour
- **S** - Slurred staccato speech, Scanning dysarthria
- **H** – Hypotonia

## Causes

- Friedreich's ataxia, ataxic telangiectasia
- neoplastic: cerebellar hemangioma
- stroke
- alcohol
- multiple sclerosis
- hypothyroidism
- **drugs: phenytoin,** lead poisoning
- paraneoplastic e.g., secondary to lung cancer

# Cerebrospinal fluid

## Normal CSF:

| | |
|---|---|
| Opening pressure | 5-18 **cm H2O** (60-150 mm) |
| Glucose | 3.3-4.4 mmol **(> 2/3 blood glucose)** |
| Protein | 0.15-0.45 g/l |
| WBC | < 5/ **mm³** |

### The characteristic cerebrospinal fluid (CSF) findings in meningitis:

| | Bacterial | Viral | Tuberculous |
|---|---|---|---|
| **Appearance** | Cloudy | Clear/cloudy | Fibrin web |
| **Glucose** | Low (< 1/2 plasma) | Normal* | Low (< 1/2 plasma) |
| **Protein** | High (> 1 g/l) | Normal/raised | High (> 1 g/l) |
| **White cells** | 10 - 5,000 polymorphs/mm³ | 15 - 1,000 **lymphocytes**/mm³ | 10 - 1,000 **lymphocytes**/mm³ |

### The following conditions are associated with raised lymphocytes:

- **Viral** meningitis/encephalitis
- **TB** meningitis
- **Partially** treated **bacterial** meningitis
- **SLE**

- Behcet's
- Leukaemia
- Lymphoma
- Lyme disease

**The following conditions are associated with raised protein levels:**

- **Bacterial**, **Tuberculous**, **Fungal** meningitis
- **Viral** encephalitis
- **GBS** (Guillain-Barre syndrome)
- **Spinal block** (Froin's syndrome): It describes an increase in CSF protein below a spinal canal blockage (e.g. tumour, disc, infection).

describes an increase in CSF protein below a spinal canal blockage (e.g. tumour, disc, infection)

The Ziehl-Neelsen stain is only 20% sensitive in the detection of tuberculous meningitis and therefore **PCR** is sometimes used (sensitivity = 75%).

Mumps is unusual in being associated with a low glucose level in a proportion of cases. A low glucose may also be seen in herpes encephalitis

## Friedreich's ataxia

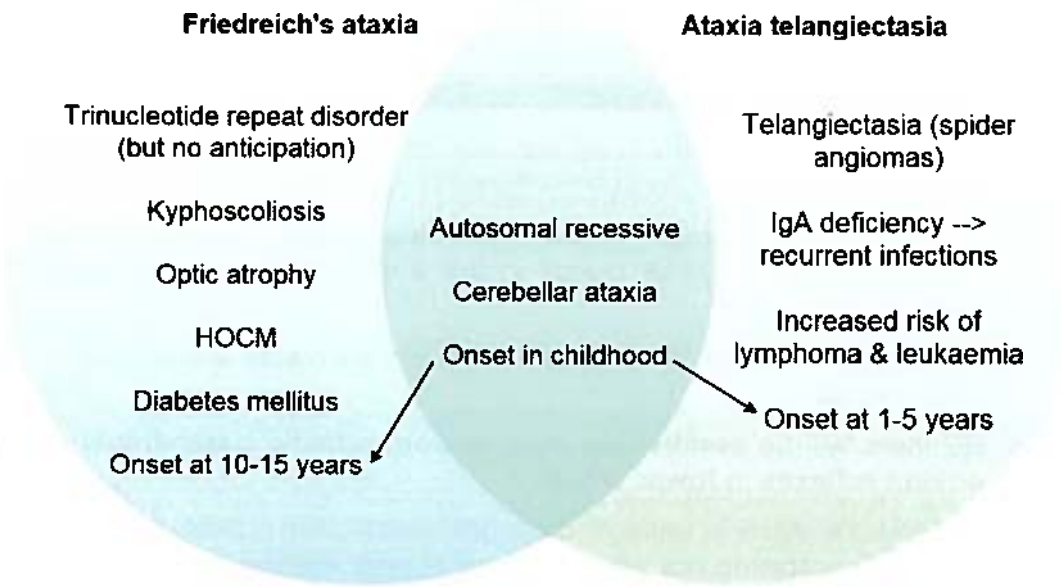
- Friedreich's ataxia is the most common of the **early-onset hereditary** ataxias.
- It is an **autosomal recessive**; trinucleotide repeat disorder characterised by a GAA repeat in the X25 gene on chromosome 9 (frataxin).
- **Neurodegeneration** of **cerebellum, Pyramidal tracts** and **dorsal root ganglia**.
- So there will be **cerebellum dysfunction**, **spastic paraparesis** and **absent reflexes in lower limbs.**
- Friedreich's ataxia is unusual amongst trinucleotide repeat disorders in **not demonstrating the phenomenon of anticipation.**
- The typical age of onset is **10-15 years old**.

## Neurological features:

- Gait ataxia and **Kyphoscoliosis** ± bilateral **pes cavus** are the most common presenting features.
- **Cerebellar ataxia** (Dysarthria, Nystagmus).
- **Optic atrophy**
- **Pyramidal weakness:**
- **Extensor plantars response with absent ankle jerks.**
- Sensory-motor neuropathy
- Spinocerebellar tract degeneration

## Other features:

- **HOCM** Hypertrophic obstructive cardiomyopathy (**90%**, **most common cause of death**)
- **DM Diabetes mellitus** (10-20%)
- **High-arched palate**




Comparison of Friedreich's ataxia and ataxia telangiectasia. Note in particular how ataxia telangiectasia tends to present much earlier, often at the age of 1-2 years

# Multiple Sclerosis (MS)

**please refer to Medscape updates in January 2022**

It is an **UMNL**.

It is also known as **disseminated** sclerosis or encephalomyelitis disseminate.

It is an **autoimmune** disease in which the body's immune system attacks his own **CNS** (**brain** and **spinal cord**) leading to **demyelination** of the CNS and hence **UMNL** signs are seen.

Onset usually occurs in **young adults**, more common in **females**.

Patients with multiple sclerosis may present with non-specific features, for example around **75%** of patients have **significant lethargy**.

Remember that **MS** affects the **CNS**, whereas **SCD** subacute combined degeneration of the cord **affects central and peripheral nerves**.

Remember that **MS** is a **central nervous system (CNS)** disorder causing **UMNL findings only**.
**NB:** Fasciculations are a LMNL finding hence MS cannot be the cause of the patient's fasciculations.

## Epidemiology

- 3 times more common in women
- most commonly diagnosed in people aged 20-40 years
- much more common at higher latitudes (5 times more common than in tropics)

## Genetics

- monozygotic twin concordance = 30%
- dizygotic twin concordance = 2%

## Subtypes

### Relapsing-remitting:

- characterized by unpredictable relapse followed by periods of months to years of relative quiet (remission) with no new signs of disease activity.
- Deficits suffered during attacks may either resolve or leave sequelae.
- This describes **the initial course of 85-90% of individuals with MS.**
- When deficits always resolve between attacks it is referred to as benign MS.

**Primary progressive:**

- about 10-15% of individuals who never have remission after their initial MS symptoms.
- It is characterized by progression of disability from onset with no or only occasional minor remission and improvements.
- The age of onset of that type is later than other types.

**Secondary progressive:**

- those with initial relapsing remission MS who then begin to have progressive neurological decline between acute attacks without any definite periods of remission.
- The median time between disease onset and conversion from relapsing-remission to secondary progressive type is 19 years.

**Progressive relapsing:**

- those who from onset have a steady neurologic decline but also suffer clear superimposed attacks.
- It the least common type.

**Non-standard behaviours**

## Features:

**Visual:**

- Optic neuritis: common presenting feature
- Optic atrophy
- **Central scotoma**
- **Uhthoff's phenomenon**: worsening of vision and feeling dizzy following rise in body temperature (e.g., during a hot bath).
- Internuclear ophthalmoplegia.

**Motor:**

- **Spastic weakness**: most commonly in the **legs** (NO HYPOTONIA).
- Patellar clonus
- Positive planters
- Brisk reflexes

**Sensory:**

- Pins/needles
- Numbness
- Trigeminal neuralgia
- **Lhermitte's syndrome**: Paraesthesia in limbs on neck flexion

### Cerebellar:

- Ataxia: more often seen during an acute relapse than as a presenting symptom.
- Tremor.

### Others:

- Urinary incontinence/ retention
- Sexual dysfunction
- Intellectual deterioration.

## Diagnosis:

### Imaging

**The following organizations have issued guidelines for the use of imaging in the diagnosis of MS**

- Consortium of Multiple Sclerosis Centers (CMSC)
- MAGNIMS (Magnetic Resonance Imaging in MS) Network
- European Academy of Neurology (EAN)

Although MRI alone cannot be used to diagnose MS, all four guidelines (MAGNIMS has two) concur that it is the imaging procedure of choice for confirming MS and monitoring disease progression in the brain and spinal cord.

**Consortium of Multiple Sclerosis Centers (CMSC)**

- CMSC revised guidelines recommend using higher-resolution three-dimensional (3D) imaging over two-dimensional (2D) imaging whenever possible.

Recommended studies for patients with CIS or suspected MS include the following:

Brain MRI protocol with gadolinium at baseline,
Add:

- Spinal cord MRI if transverse myelitis, inconclusive brain MRI, or age older than 40 with non-specific brain MRI findings
- Cervical cord MRI performed simultaneously with brain MRI is advantageous in patients with or without transverse myelitis
- Orbital MRI if severe optic neuritis with poor recovery

Recommended schedules for follow-up brain MRI in patients with a CIS or suspected MS are as follows:

- 6–12 months for high-risk CIS (≥2 ovoid lesions on first MRI)

- 12–24 months for low-risk CIS (normal brain MRI findings) and/or uncertain clinical syndrome with suspicious brain MRI features (e.g., radiologically isolated syndrome [RIS])

Follow-up brain MRI with gadolinium is recommended for patients with an established diagnosis of MS in the following circumstances:

- No recent prior imaging available (e.g., patient with MS transferring to a new clinic)
- Postpartum, to establish a new baseline.
- Prior to starting or switching disease-modifying therapy.
- Approximately 6 months after switching disease-modifying therapy, to establish a new baseline on the new therapy
- Every 1–2 years while on disease-modifying therapy, to assess subclinical disease activity
- In the event of unexpected clinical deterioration or reassessment of original diagnosis

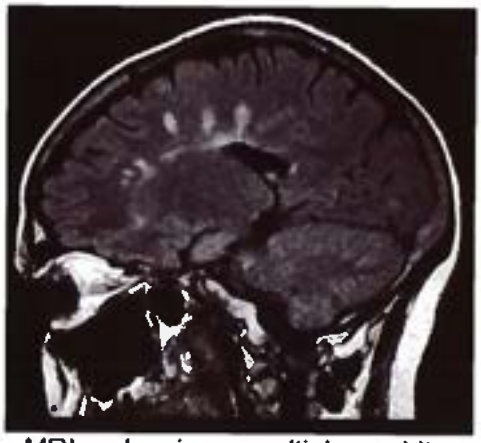
In addition, brain MRI is recommended to monitor for progressive multifocal leukoencephalopathy (PML) at the following intervals:

- Every 12 months for patients negative for serum JC virus antibody
- Every 3–6 months for patients positive for serum JC virus antibody treatment and treatment duration with natalizumab ≥18 months

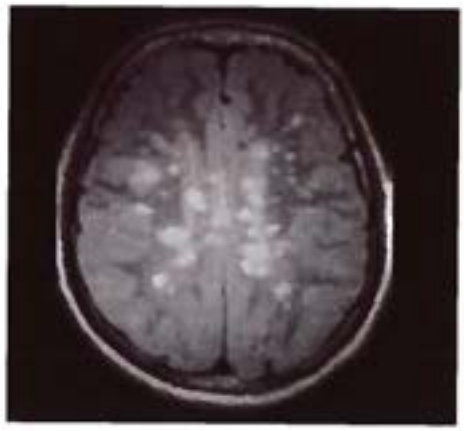
The gold standard for diagnosis of MS remains clinical assessment, with evidence of **white matter** symptoms and signs **disseminated in time and space**.

**MRI** is the investigation which will show **periventricular white matter plaques** of **different ages** and in **different locations**, to add weight to the clinical assessment.

CT brain will not show these changes.

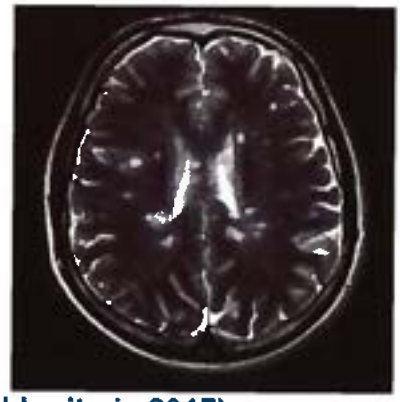


MRI showing multiple white matter plaques penpendicular to the corpus callosum giving the appearance of Dawson fingers



MRI FLAIR from the same patient as above. The numerous lesions are more easily identified than in the above T2 image.

MRI from a young patient with multiple sclerosis. Widespread periventricular, juxtacortical, post fossa and upper cervical cord high T2 regions are noted. Note the difference in the lesions with varying degrees of contrast enhancement and restricted diffusion indicating active/recent demyelination. This satisfies the diagnostic criteria in terms of separation in terms of time space.



**Diagnostic criteria (Revised McDonald criteria 2017):**
**used to diagnose MS based on the dissemination of the CNS lesions in time and space.**

**Dissemination in time (DIT): appearance of new lesions over time**

- Criterion met (2 2 exacerbations) occurring at least 30 days apart
- Criterion not met (1 exacerbation)diagnosis requires confirmation of DIT by one of the following:
  - An additional exacerbation
  - MRI that demonstrates the presence of both gadolinium-enhancing and nonenhancing lesions at any time or a new hyperintense T2 or enhancing lesion on follow-up MRI
  - Oligoclonal bands in the CSF

**Dissemination in space (DIs) on MRI: presence of lesions in different regions of the CNS**

- Criterion met (2 lesions with objective clinical evidence) of the 4 MS-typical regions of CNS (periventricular, juxtacortical, infratentorial, or spinal cord)
- Criterion not met (1 lesion with objective clinical evidence) →diagnosis requires confirmation of DIS by one of the following:
  - An additional exacerbation with presence of one more lesion with objective Clinical evidence involving a different CNS region
  - Presence on MRI of 1 T2-hyperintense lesion in at least 2 of the following regions periventricular, juxtacortical, infratentorial, spinal

## Investigation:

(demonstration of lesions disseminated in time and place):

**1) MRI (Brain & Spinal cord):**

i. High signal T2 lesions.
ii. Periventricular **plaque**.
iii. Dawson fingers: often seen on FLAIR images - hyperintense lesions penpendicular to the corpus callosum

**2) CSF:**

i. **Oligoclonal bands** (not in serum)
ii. ↑ Intrathecal synthesis of IgG

**3) VEP (visual evoked potential):**

i. **Delayed**, but well-preserved wave form.

## Treatment in multiple sclerosis:

- Treatment and management of multiple sclerosis should be targeted toward relieving symptoms of the disease, treating acute exacerbations, shortening the duration of an acute relapse, reducing frequency of relapses, and preventing disease progression.
- Drugs approved for use in MS that reduce the frequency of exacerbations or slow disability progression are referred to as disease-modifying drugs (DMDs).
- These DMDs can be further classified as immunomodulating (or receptor modulating) or immunosuppressives.
- Some immunosuppressants are also FDA-approved as antineoplastic agents.
- Drugs that treat MS-related symptoms (eg, acute exacerbations, cognitive dysfunction, fatigue, spasticity, bowel and bladder problems, and pain) but do not modify the course of the disease are referred to as symptom-management medications.

### European Committee for Research and Treatment of Multiple Sclerosis (ECTRIMS) and the European Academy of Neurology (EAN)

- In 2017, the ECTRIMS and EAN released the first set of guidelines on the use of disease-modifying therapies in multiple sclerosis.
- The European guidelines cover the treatment of adults with MS or clinically isolated syndrome (CIS), the monitoring of treatment response, the stopping and switching of treatment strategies, and treatment in special situations, such as pregnancy.
- There are 20 main recommendations.
- Those with strong evidence include the following:
- Offer interferon or glatiramer acetate to patients with CIS and abnormal MRI findings with lesions suggesting MS who do not fulfill full criteria for MS.
- Offer early treatment with disease-modifying drugs in patients with active relapsing-remitting MS (RRMS), as defined by clinical relapses and/or MRI activity (active lesions: contrast-enhancing lesions; new or unequivocally enlarging T2 lesions assessed at least annually).
- Offer a more efficacious drug to patients treated with interferon or glatiramer acetate who show evidence of disease activity.

## Acute relapse:

- High dose steroids (e.g. **oral or IV methylprednisolone**) may be given **for 3-5 days** to shorten the length of an acute relapse.
- It should be noted that **steroids shorten the duration of a relapse and do not alter the degree of recovery (i.e. whether a patient returns to baseline function).**

## Disease modifying drugs:

### Class Summary

- Immunomodulators or receptor modulators are indicated for the treatment of patients with relapsing forms of MS.
- They help to slow the accumulation of physical disability and decrease the frequency of clinical exacerbations.

### Interferon beta-1b (Betaseron, Extavia)

- Interferon beta-1b was the first medication approved by the FDA for MS.
- It is approved for the treatment of relapsing forms of MS to reduce the frequency of clinical exacerbations.

- It has shown efficacy in patients who have experienced a first clinical episode and have MRI features consistent with MS.
- The exact mechanism by which interferon beta-1b exerts its effects is unknown.
- Interferon beta inhibits the expression of pro-inflammatory cytokines, including interleukin (IL)-1 beta, tumor necrosis factor (TNF)-alpha and TNF-beta, interferon gamma (IFN-γ), and IL-6. IFN-γ is believed to be a major factor responsible for triggering the autoimmune reaction leading to MS.

**Interferon beta-1a (Avonex, Rebif)**

- Interferon beta-1a is approved for the treatment of patients with relapsing forms of MS. It helps to slow the accumulation of physical disability and decrease the frequency of clinical exacerbations.
- The exact mechanism by which interferon beta-1a exerts its effects is not fully defined. Interferon beta inhibits the expression of proinflammatory cytokines, including interferon gamma (IFN-γ), which is believed to be a major factor responsible for triggering the autoimmune reaction leading to MS.

**Alemtuzumab (Lemtrada)**

- Alemtuzumab is a recombinant monoclonal antibody against CD52 (lymphocyte antigen).
- This action promotes antibody-dependent cell lysis. It is indicated for relapsing forms of multiple sclerosis. Because of the risk for severe and lasting autoimmune adverse effects, use is reserved for patients who have an inadequate response to 2 or more other drugs for MS.

**Peginterferon beta-1a (Plegridy)**

- Precise mechanism by which peginterferon beta-1a exerts its effects in patients with multiple sclerosis is unknown.
- Interferons are thought to alter response to surface antigen and may enhance immune cell activities.
- It is indicated for treatment of relapsing forms of multiple sclerosis.

**Natalizumab (Tysabri)**

- Natalizumab is indicated as monotherapy for MS to delay the accumulation of physical disability and reduce the frequency of clinical exacerbations.
- Natalizumab is a recombinant humanized monoclonal antibody that binds with alpha-4 integrins and inhibits their adherence to their counterreceptors.

- The specific mechanism by which natalizumab exerts its effects in MS has not been defined.
- Natalizumab has a black-box warning for progressive multifocal leukoencephalopathy (PML).
- Because of the risk of PML, natalizumab is available only through a special restricted distribution prescribing program called the Tysabri Outreach Unified Commitment to Health (TOUCH).

**Glatiramer acetate (Copaxone, Glatopa)**

- Glatiramer acetate is approved for the reduction of the frequency of relapses in patients with relapsing-remitting MS, including patients who have experienced a first clinical episode and have MRI features consistent with MS.
- Glatiramer acetate's mechanism of action is unknown, but this agent is thought to modify immune processes believed to be responsible for the pathogenesis of MS.
- The recommended dosage is 20 mg/day administered subcutaneously.
- The sites for injection include the arms, abdomen, hips, and thighs.

**Teriflunomide (Aubagio)**

- Teriflunomide is an oral immunomodulatory agent that elicits anti-inflammatory effects by inhibiting dihydroorotate dehydrogenase, a mitochondrial enzyme involved in pyrimidine synthesis.
- It is indicated for relapsing forms of MS.

**Dimethyl fumarate (Tecfidera)**

- Dimethyl fumarate (DMF) is an oral Nrf2 pathway activator indicated for relapsing forms of multiple sclerosis.
- DMF is metabolized rapidly by presystemic hydrolysis by esterase in the GI tract, blood, and tissues (before it reaches systemic circulation) and is converted to its active metabolite, monomethyl fumarate (MMF).
- MMF activates the nuclear factor (erythroid-derived 2)-like 2 (Nrf2) pathways, a transcription factor encoded by the *NFE2L2* gene.
- The Nrf2 antioxidant response pathway is a cellular defense against oxidative stress.
- MMF has been identified as a nicotinic acid receptor agonist in vitro.

**Monomethyl fumarate (Bafiertam)**

- Monomethyl fumarate (MMF) is the active metabolite of prodrug dimethyl fumarate (DMF). Following oral administration, 190 mg of MMF is bioequivalent to 240 mg of DMF.

- It is indicated for adults with relapsing forms of multiple sclerosis, to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease.

**Ocrelizumab (Ocrevus)**

- Ocrelizumab is a humanized monoclonal antibody designed to selectively target CD20, a cell surface antigen present on pre-B and mature B lymphocytes.
- Following cell surface binding to B lymphocytes, ocrelizumab results in antibody-dependent cellular cytolysis and complement-mediated lysis.
- Following 2 initial IV doses administered 2 weeks apart, subsequent IV doses are administered every 6 months.
- It is indicated for adults with relapsing or primary progressive forms of multiple sclerosis.

**Kesimpta (ofatumumab SC)**

- Ofatumumab is an anti-CD20 monoclonal antibody administered subcutaneously via once-monthly injection.
- The exact mechanism of action for RMS is unknown.
- It is presumed to involve binding to CD20, a cell surface antigen present on pre-B and mature B lymphocytes.
- The cell surface binding to B lymphocytes results in antibody-dependent cellular cytolysis and complement-mediated lysis.
- It is indicated for relapsing forms of MS, to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease.

**Sphingosine 1-Phosphate Receptor Modulators Class Summary:**

- Sphingosine-1-phosphate (S1P) receptor modulators bind with high affinity to S1P receptors 1 and 5.
- This action blocks lymphocytes to egress from lymph nodes, therefore reducing the number of lymphocytes in peripheral blood.
- The precise mechanism by which SP1 receptor modulators exert therapeutic effects in MS is unknown, but may involve reduction of lymphocyte migration into the central nervous system.

**Examples are:**

**Siponimod (Mayzent)**

**Fingolimod (Gilenya, Tascenso ODT)**

### Ozanimod (Zeposia)

- S1P receptor modulator.
- It is indicated for treatment relapsing forms of multiple sclerosis (MS), including clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease.

## Problem oriented treatment:

### Fatigue

- once other problems (e.g. anaemia, thyroid or depression) have been excluded NICE recommend a trial of amantadine
- other options include mindfulness training and CBT

### Spasticity:

- **Baclofen** and **gabapentin** are first-line.
- Other options include diazepam, Dantrolene and tizanidine.
- Physiotherapy is important
- Cannabis and Botox are undergoing evaluation.
- Hallucinations are occasionally seen on the baclofen withdrawal.

### Bladder dysfunction:

- May take the form of urgency, incontinence, overflow etc.
- Guidelines stress the importance of getting an ultrasound first to assess bladder emptying - anticholinergics may worsen symptoms in some patients.
- If significant residual volume → intermittent self-catheterisation.
- If no significant residual volume → anticholinergics may improve urinary frequency.

**Oscillopsia** (visual fields apper to oscillate)

- gabapentin is first-line

## Good prognosis features:

- **Female** sex
- **age: young age of onset (i.e. 20s or 30s)**
- **Relapsing-remitting** disease
- **sensory symptoms only**
- **Long interval** between first two relapses
- complete recovery between relapses

**Ways of remembering prognostic features that:**
the **typical** patient carries a **better** prognosis than an atypical presentation.

# Guillain-Barre syndrome (GBS): (Post-infectious polyradiculopathy)

It is an **immune**-mediated **acute inflammatory demyelinating polyneuropathy**.

GBS describes an immune mediated **demyelination** of the **peripheral** nervous system often triggered by an **infection** such as **viral** (CMV), viral pneumonia or **bacterial** (classically **Campylobacter jejuni**).

GBS is a **post-infectious acute polyneuritis** typified by **elevated CSF protein** with few cells and often normal glucose.

## Pathogenesis:

- Cross reaction of antibodies with gangliosides in the peripheral nervous system.
- Correlation between anti-ganglioside antibody (e.g. anti-GM1) and clinical features has been demonstrated.
- **Anti-GM1 antibodies in 25%** of patients.

## Features

### characteristic features

- **progressive weakness** of **all four limbs**.The weakness is classically **ascending** i.e., the **lower extremities** are affected first, however it tends to affect **proximal** muscles earlier than the distal ones.
- **Ascending symmetrical progressive weakness and numbness** affecting initially the **legs** and extending to involve the upper limb.
- Weakness begins in the legs and progressively ascends to involve the trunk, upper limbs and finally the bulbar muscles (**Landry's ascending paralysis**).
- Asymmetry is present in only 9% of patients, with **symmetrical** involvement being **typical**.
- Sensory symptoms tend to be mild (e.g. distal paraesthesia, peripheral sensory neuropathy) with **very few sensory signs (NO sensory loss).**
- Usually there is **painless** progression over days or weeks, but in cases of abrupt onset, there may be tenderness or muscle pain.

Some patients experience back pain in the initial stages of the illness.

### Other features:

- **Areflexia** (All tendon reflexes are absent and the plantar responses ware flexor).
- Cranial nerve involvement e.g., diplopia.
- **Autonomic** dysfunction: e.g. **urinary retention** and **postural hypotension& tachycardia**.
- **CSF protein is elevated** to more than **twice** the upper limit of normal, with normal glucose and no pleocytosis. Bacterial cultures are negative and viral cultures rarely isolate anything.
- The **dissociation between a high CSF protein**, **normal** glucose and a lack of CSF cellular response in a **person with an acute or subacute polyneuropathy** is **diagnostic** of Guillain-Barre syndrome.
- Although LP is an important part of GBS assessment, a normal CSF protein does not exclude the condition.

### Less common findings:

- Papilledema: thought to be secondary to reduced CSF resorption.
- nerve conduction studies may be performed.
  - decreased motor nerve conduction velocity (due to demyelination)
  - prolonged distal motor latency
  - increased F wave latency

**EX**: A 50-year-old woman with a 2 week history of difficulty walking and weakness in her arms.

O/E, there was **proximal** and distal limb weakness which was more marked in the **legs** than the arms. **All tendon reflexes were absent** and **the plantar responses were flexor**. There was **no sensory loss**.

BP in the supine position was 140/78 mmHg & was 110/70 mmHg on standing.

What is the most likely diagnosis >>> classical presentation of **Guillain-Barre**

## Complications include:

- **Bulbar** involvement occurs in **50%,** with a risk of aspiration and respiratory insufficiency which can be problematic.
- In **20%** of cases there is **urinary incontinence or retention**.

## Miller Fisher syndrome

- It is a variant of Guillain-Barre syndrome (**GBS**)
- Associated with **ophthalmoplegia** and **ataxia**.
- **The eye muscles are typically affected first.**
- Usually presents as a **descending** paralysis rather than ascending as seen in other forms of Guillain-Barre syndrome.
- **anti-GQ1b antibodies are present in 90% of cases**
- **Anti-GQ1b antibodies** are present in **95%** of cases (highly specific).

**Bickerstaff's encephalitis** is like Miller-Fisher **BUT** there are **drowsiness** and **brisk reflexes**.

## Management:

- **Plasma exchange**
- **IVIG** (IV immunoglobulins) **0.5 g/kg/day for 5 days**: as effective as plasma exchange. No benefit in combining both treatments. IVIG may be easier to administer and tends to have fewer side-effects.

Steroids and immunosuppressants have not been shown to be beneficial.

**FVC** (Forced **vital capacity**) regularly to **monitor respiratory function.**

FVC is also the best way to monitor respiratory function in any neurological disorders that can affect the respiratory muscles (e.g. GBS, myasthenia gravis) and a better indication of the need for **ventilation**.

**FVC** is used to monitor respiratory function in **GBS**

## Prognosis:

- 20% suffer permanent disability, 5% die
- **Poor prognostic features**
  - **Age > 40 years**
  - **Previous history of a diarrhoeal illness (specifically Campylobacter jejuni)**
  - High **anti-GM1 antibody titre**
  - Poor upper extremity muscle strength
  - Need for ventilatory support
  - There is currently contradictory evidence as to whether a gradual or rapid onset of GBS is associated with a poor outcome.

**Diaphragmatic** weakness occurs in **30%** of patients with patients with GBS and involvement of the neck muscles, tongue and palate leads to further respiratory compromise.
Respiratory muscle function is best monitored by frequent assessment of the forced vital capacity (**FVC**).
**ITU** admission is recommended when **FVC is less than 20 mL/kg** and **intubation** is recommended in most cases when **FVC is less than 15 mL/kg**.

**EX**: A **female** patient aged **30** has a **5 year history** of difficulty getting upstairs and out of a low chair and mild upper limb weakness but no pain. There is no family history. She presented with severe **type 2 respiratory failure**. **EMG** showed evidence of **myopathy**. Which is the most likely diagnosis?
**Acid maltase deficiency** typically presents with **insidious onset** of **proximal myopathy** and **early respiratory muscle weakness**.

**NB**: **Botulism**: have the same clinical presentation of **descending weakness** (i.e. opposite in direction of GBS) with **autonomic dysfunction** (fixed dilated pupils).
It is a **neuromuscular junction disorder** and therefore nerve conduction studies and EMG are normal.
**Repetitive nerve stimulation shows incremental responses**, is diagnostic of botulism.

**NB**: **CIDP** (**Chronic inflammatory demyelinating polyneuropathy**) is clinically similar to **GBS** (hyporeflexia or areflexia, paraesthesia and mild sensory deficits in the upper and lower extremities, weakness) except that it follows a **chronic progressive course**.

**MRCPUK part 1 exam:** Regarding nerve conduction studies for suspected Guillain-Barre syndrome. Which finding would be most consistent with this diagnosis? **Reduced conduction velocity**

**MRCPUK part 1 exam:** a patient developed weakness in his legs extended to his arms after viral illness. ↓↓ power, reflexes and sensation in his lower limbs. Developed SOB &↓↓ (FVC). Given the likely diagnosis, what is the treatment of choice? **Intravenous immunoglobulin**
(Guillain-Barre syndrome (GBS) secondary to a viral illness, possibly the **Epstein-Barr virus**)

**MRCPUK part 1 exam:** H/O double vision & ↓↓ eye movement + unsteadiness + ↓↓ reflexes + past-pointing. What is the most likely diagnosis? **Miller Fisher syndrome**

## Neuropathic pain

Neuropathic pain may be defined as pain which arises following damage or disruption of the nervous system.

**It is often difficult to treat and responds poorly to standard analgesia.**

### Examples include:

- Diabetic neuropathy
- Post-herpetic neuralgia
- Trigeminal neuralgia
- Prolapsed intervertebral disc

**NICE updated their guidance on the management of neuropathic pain in 2013:**

- first-line treatment*: **amitriptyline, duloxetine, gabapentin or pregabalin**
  - if the first-line drug treatment does not work try one of the other 3 drugs
  - in contrast to standard analgesics, drugs for neuropathic pain are typically used as monotherapy, i.e. **if not working then drugs should be switched, not added**
- **tramadol** may be used as 'rescue therapy' for exacerbations of neuropathic pain
- topical capsaicin may be used for localised neuropathic pain (e.g. post-herpetic neuralgia)
- pain management clinics may be useful in patients with resistant problems

NICE issued guidance in 2010 on the management of neuropathic pain:

- First-line treatment*: oral **Amitriptyline** or **Pregabalin.**
- If satisfactory pain reduction is obtained with amitriptyline but the person cannot tolerate the adverse effects (it is better to avoid **amitriptyline** in pt. with **BPH** due to the risk of **urinary retention**), consider oral imipramine or nortriptyline as an alternative.

- Second-line treatment: if first-line treatment was with amitriptyline, switch to or combine with pregabalin. If first-line treatment was with pregabalin, switch to or combine with amitriptyline.
- Other options: pain management clinic, **tramadol** (no other strong opioids), topical lidocaine for localised pain if patients unable to take oral medication.

Please note that for some specific conditions the guidance may vary. For example:

- **Duloxetine** for **diabetic neuropathy.**
- **Carbamazepine** is used first-line for **trigeminal neuralgia**.

## Hereditary Sensorimotor Neuropathy (HSMN)

It is a relatively new term which encompasses **Charcot-Marie-Tooth disease** (also known as **perineal muscular atrophy**).

Over 7 types have been characterised - however only 2 are common clinically:

- HSMN **type I:** primarily due to **demyelinating** pathology
- HSMN **type II**: primarily due to **axonal** pathology

### HSMN type I:

- **Autosomal dominant,** so **50%** of children will be affected.
- Due to defect in PMP-22 gene (which codes for myelin).
- Features often start at puberty.

### Features:

- There may be a history of frequently sprained ankles
- Hyporeflexia
- Stork leg deformity
- **Motor** symptoms predominate.
- **Distal muscle wasting, pes cavus (high arched foot), clawed toes.**
- **Foot drop, leg weakness** often **first** features.
- Nerve Conduction Velocity **(NCV) < 30 m/sec.**

# Peripheral neuropathy

**Please refer to nice guidelines on neuropathic pain 2020.**
The International Association for the Study of Pain (IASP 2011) defines **neuropathic pain as:**'pain caused by a lesion or disease of the somatosensory nervous system'.
Central neuropathic pain is defined as 'pain caused by a lesion or disease of the central somatosensory nervous system', and peripheral neuropathic pain is defined as 'pain caused by a lesion or disease of the peripheral somatosensory nervous system'.

**It may be divided into conditions which predominately cause a motor or sensory loss.**

| Predominately motor loss | Predominately sensory loss |
|---|---|
| • GBS.<br>• CIDP.<br>• HSMN<br>• Porphyria.<br>• Lead poisoning<br>• Diphtheria | • DM.<br>• Alcoholism.<br>• Vit B12 deficiency.<br>• Uraemia.<br>• Amyloidosis.<br>• Leprosy. |

### Alcoholic neuropathy:

- Secondary to both direct toxic effects and reduced absorption of Vit. B.
- Sensory symptoms typically present prior to motor symptoms.

### Vitamin B12 deficiency:

- Subacute combined degeneration (SCD) of spinal cord.
- Dorsal column usually affected first (joint position, vibration) prior to distal paraesthesia.

## Treatment

**All neuropathic pain (except trigeminal neuralgia):**

- Offer a choice of amitriptyline, duloxetine, gabapentin or pregabalin as initial treatment for neuropathic pain (except trigeminal neuralgia)
- If the initial treatment is not effective or is not tolerated, offer one of the remaining
- drugs, and consider switching again if the second and third drugs tried are also not effective or not tolerated.
- Consider tramadol only if acute rescue therapy is needed.

- Consider capsaicin cream for people with localized neuropathic pain who wish to avoid, or who cannot tolerate, oral treatments.

Duloxetine was licensed for diabetic peripheral neuropathic pain only, and gabapentin was licensed for peripheral neuropathic pain only, so use for other conditions was off label.

**N.B.** Combination therapy is commonly prescribed for neuropathic pain. It may also be a helpful option as a stepwise approach if initially used drugs are insufficient at reducing pain.

Combination therapy may also result in better tolerability because smaller doses of individual drugs are often used when combined with other drugs. However, there is a lack of trial evidence comparing the clinical and cost effectiveness and tolerability of different drug combinations.

Further research should be conducted:

### Trigeminal neuralgia:

Offer carbamazepine as initial treatment for trigeminal neuralgia.

If initial treatment with carbamazepine is not effective, is not tolerated or is contraindicated, consider seeking expert advice from a specialist and consider early referral to a specialist pain service or a condition-specific service.

## Nerve conduction studies (NCS)

It is useful in determining between axonal and demyelinating pathology

| Axonal | Demyelinating |
|---|---|
| ➢ Normal conduction velocity<br>➢ Reduced amplitude | ➢ Reduced conduction velocity<br>➢ Normal amplitude |

| | Axonal | Demyelinating |
|---|---|---|
| Conduction velocity | Normal | Reduced |
| Amplitude | Reduced | Normal |

# Absent ankle jerks, extensor plantars

Typically caused by lesion producing both upper motor neuron (extensor plantars) and lower motor neuron (absent ankle jerk) signs

## Causes

- subacute combined degeneration of the cord
- motor neuron disease
- Friedreich's ataxia
- syringomyelia
- taboparesis (syphilis)
- conus medullaris lesion

**Absent ankle jerks** may occur in conditions associated with neuropathy:

- **B12 deficiency**,
- **SLE**,
- **Tabes dorsalis (Syphilis)**
- **Cerebrotendinous xanthomatosis**

**Cerebrotendinous xanthomatosis** is an inherited condition, associated with accumulation of cholesterol in tissues including brain, peripheral nerve and tendons which produces a clinical picture of:

- Early onset dementia
- Gait ataxia
- Loss of vibration sense
- Cataracts
- Large tendon xanthomata.
- There is a deficiency in sterol storage, and diagnosis is based on **high serum (and tendon)** cholesTANOL. BUT Serum cholesterol may be normal or low.
- It is eminently treatable by the oral chenodeoxycholic acid.

**EX**: A 39-year-old woman is found to have **absent ankle jerks** and **gait disturbance** >>> so should check: **ANA, B12, VDRL, Cholestanol levels**

## Extensor plantars and absent ankle jerks (Lesions that produce both UMNL and LMNL)

Typically caused by **lesion** producing **both UMNL** (extensor plantars) and **LMNL** (absent ankle jerk) signs.

### Causes:

- **SCD** (Subacute combined degeneration of the cord)
- **MND** (Motor neuron disease)
- **Friedreich's ataxia**
- **Syringomyelia, Syringobulbia.**
- **Taboparesis (syphilis)**
- Conus medullaris lesion

## Peripheral neuropathy demyelinating vs. axonal

### Axonal pathology:

- **Alcohol**
- **DM** (± a demyelinating picture)
- **Vit B12** deficiency (± a demyelinating picture)
- **Vasculitis**
- **Renal failure.**
- HSMN type II

### Demyelinating pathology:

- **GBS** (Guillain-Barre syndrome)
- **CIDP** (Chronic inflammatory demyelinating polyneuropathy).
- Paraprotein neuropathy
- Amiodarone
- HSMN type I

## Drugs causing peripheral neuropathy

### Drugs causing a peripheral neuropathy:

- **Antibiotics: Nitrofurantoin, Metronidazole**
- **Amiodarone**
- **Isoniazid**
- **Vincristine** & most chemotherapy
- **TCA** (Tricyclic antidepressants)

## Autonomic neuropathy

### Features:

- Impotence,
- Urinary retention.
- Postural hypotension e.g. drop of 30/15 mmHg
- Inability to sweat
- Loss of decrease in heart rate following deep breathing
- Pupils: dilates following adrenaline instillation

### Causes:

- **DM**
- **GBS** (Guillain-Barre syndrome)
- **Parkinson's**
- **MSA** (Multisystem atrophy)(Shy-Dragger syndrome)
- Infections: **HIV**, Chagas' disease, neurosyphilis
- Drugs: antihypertensives, TCA
- Craniopharyngioma

## Meralgia paraesthetica

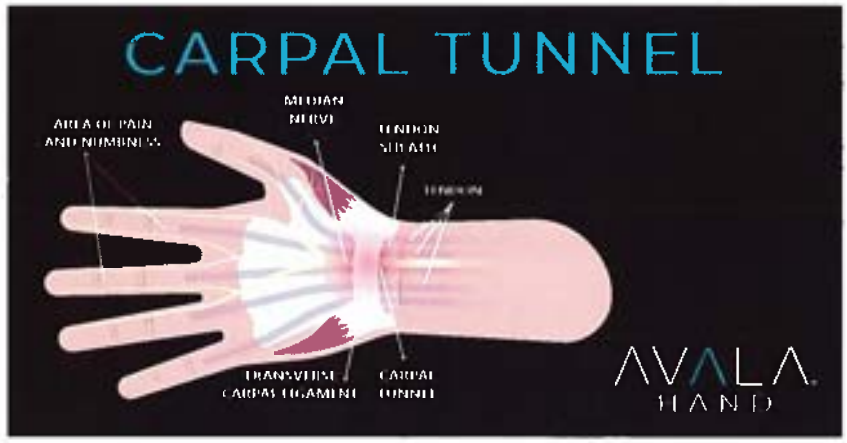
- Caused by compression of **lateral cutaneous nerve of thigh.**
- Typically burning sensation over antero-lateral aspect of thigh.

Burning thigh pain >>? Meralgia paraesthetica >> lateral cutaneous nerve of thigh compression.

**MRCPUK part 1 exam: A patient presents with a burning sensation over antero-lateral aspect of thigh. Which nerve is most likely to be affected?**
**>> Lateral cutaneous nerve of thigh**

# Carpal tunnel syndrome

It is caused by compression of median nerve in the carpal tunnel.




## History:

- Pain/pins and needles in thumb, index, middle finger
- Unusually the symptoms may 'ascend' proximally
- Classically **at night**
- **Patient shakes his hand to obtain relief (WAKE AND SHAKE).**

## Examination:

- **Weakness of thumb abduction** (abductor pollicis brevis)
- **Wasting of thenar eminence** (NOT hypothenar)
- **T**inel's sign: **T**apping causes paraesthesia
- Phalen's sign: flexion of wrist causes symptoms

The median nerve also supplies **most of the muscles of the thenar eminence**, namely the (LOAF):

- **L**ateral two lumbricals
- **O**pponens pollicis
- **Ab**ductor pollicis brevis, and
- **F**lexor pollicis brevis

**NB:** The remaining small muscles of the hand are supplied by the ulnar nerve.

## Causes:

- Idiopathic
- Pregnancy
- Oedema e.g., heart failure
- Lunate fracture
- **Rheumatoid arthritis**

### Electrophysiology:

- Motor + sensory: prolongation of the action potential
- **The most appropriate further investigation ► Electromyogram (EMG) / nerve conduction studies**

### Treatment:

- Corticosteroid injection
- Wrist splints at night
- Surgical decompression (flexor retinaculum division)
- In patients with mild carpal tunnel syndrome the management should be behavior modification.

**NB: The palmar cutaneous branch** of the **median nerve** lies **superficial** to the flexor retinaculum and does **not** pass through the carpal tunnel.

It supplies the **skin over the thenar eminence**, which is therefore **spared** in carpal tunnel syndrome.

So Pt. with CTS have preserved skin sensation over thenar area.

## Saphenous nerve injury

### Overview

- Saphenous nerve is a terminal cutaneous branch of the femoral nerve.
- **It is supplies the skin over the anteromedial side of the knee, leg and medial malleolus.**
- **It is strictly a sensory nerve; it has no motor component.**
- It is commonly blocked to complement anesthesia of the lower leg.

### Causes

- Saphenous vein harvest for coronary artery bypass grafting (CABG) (most common).
- Femoral artery catheterization for angiography
- Trochanter placement during knee arthroscopy.
- Long saphenous vein stripping for varicose veins.

### Features

- **Loss of sensation over the medial aspect of the lower leg.**

## Brachial neuritis

- Brachial neuritis is characterized by acute onset of unilateral (occasionally bilateral) severe pain, followed by shoulder and scapular weakness several days later.
- Sensory changes are usually minimal.
- There may be subsequent rapid wasting of the arm muscles in accordance to which nerve is involved.
- Precipitating factors include recent trauma, infection, surgery, or even vaccination.
- Rarely it may be hereditary.
- The prognosis is usually good except when the phrenic nerve is involved since this can result in significant breathlessness.

## Brachial plexus injuries

**Erb-Duchenne paralysis**

- damage to C5,6 roots
- winged scapula
- may be caused by a breech presentation

**Klumpke's paralysis**

- **damage to T1**
- loss of intrinsic hand muscles
- due to traction

## Ulnar nerve

It arises from medial cord of brachial plexus (**C8, T1**)

The ulnar nerve supplies **all the muscles of the hands except thenar** muscles and the lateral two lumbricals which are supplied by median nerve.

**Motor: to**

- Medial two lumbricals
- Dductor pollicis >> Adduction of the thumb
- Interossei
- Hypothenar muscles: (opponens digiti minimi, abductor digiti minimi, flexor digiti minimi).
- Flexor carpi ulnaris

**Sensory to:** Medial 1 1/2 fingers (palmar and dorsal aspects)

## Patterns of damage:

### Damage at wrist:

- **'Claw hand'** - hyperextension of the metacarpophalangeal joints and flexion at the distal and proximal interphalangeal joints of the 4th and 5th digits
- Wasting and paralysis of intrinsic hand muscles (except lateral two lumbricals)
- Wasting and paralysis of **hypothenar muscles**
- **Sensory loss to the medial 1 1/2 fingers** (palmar and dorsal aspects)

### Damage at elbow:

- As above (however, **ulnar paradox** - clawing is more severe in distal lesions)
- Radial deviation of wrist

## Diagnosis:

- **Nerve conduction studies will confirm the site of the lesion.**

### Common questions about median nerve:

| Question | Answer |
|---|---|
| Rout ? | C8-T1 |
| Typical injury? | Fracture of epicondyle of humerus |
| Motor deficit? | Medial finger flexion/wrist flexion |
| Sensory deficit? | Medial 1.5 fingers/hypothenar eminence |
| Sign? | Radial deviation of wrist upon flexion/claw hand |

**MRCPUK part 1 exam: H/O dropping things on a frequent basis and muscle wasting at the back of the right hand. On examination, you note wasting of the dorsal interossei. What is the nerve supply of the dorsal interossei?** >> C8/T1

## Sciatic nerve palsy

Sciatic nerve palsy is a known complication of a **total hip replacement** (femoral nerve palsy can occur but is much less common).

It causes **global weakness of the ankle** due to the involvement of both of its branches: **tibial nerve (plantaflexion and inversion)** and **common peroneal nerve (dorsiflexion and eversion).**

The **ankle jerk is absent** due to tibial nerve involvement.

When back pain is caused by **a L5/S1 disc prolapse**, the **S1** nerve root may be affected

The **Achilles reflex tests** the **S1/2** nerve root, and sciatic nerve.

**NB: Ankle** reflex (**tibial nerve** mediated) and
**NB: Knee** reflex (**femoral nerve** mediated).
**NB: Foot drop** >>> affection of **common peroneal nerve**

## Common peroneal nerve lesion

The sciatic nerve divides into the tibial and common peroneal nerves. Injury often occurs at the neck of the fibula

The most characteristic feature of a common peroneal nerve lesion is foot drop.

### Other features include:

- **weakness of foot dorsiflexion**
- **weakness of foot eversion**
- weakness of extensor hallucis longus
- sensory loss over the dorsum of the foot and the lower lateral part of the leg
- wasting of the anterior tibial and peroneal muscles

**Hip weakness:**

- Weakness of hip **Ab**duction (Gluteus medius) >> superior gluteal nerve palsy
- Weakness of hip **ad**duction (Adductor magnus and minimus) >> Obturator nerve palsy
- Weakness of hip flexion (iliopsoas muscle) >> Femoral nerve palsy
- Weakness of hip extension (Gluteus maximus) >> inferior gluteal nerve

## Complex regional pain syndrome

Complex regional pain syndrome (CRPS) is the modern, umbrella term for a number of conditions such as reflex sympathetic dystrophy and causalgia. It describes a number of neurological and related symptoms which typically occur following surgery or a minor injury. CRPS is 3 times more common in women.

### There are two types of CRPS:

- **type I: (most common): there is no demonstrable lesion to a major nerve**
- **type II:** there is a lesion to a major nerve

### Features

- progressive, disproportionate symptoms to the original injury/surgery
- allodynia
- temperature and skin colour changes
- oedema and sweating
- motor dysfunction
- the Budapest Diagnostic Criteria are commonly used in the UK

### Management

- early physiotherapy is important
- neuropathic analgesia in-line with NICE guidelines
- specialist management (e.g. Pain team) is required

## Cervical spondylitic myelopathy

- Cervical spondylosis is a degenerative condition affecting the cervical spine, **essentially osteoarthritis of the cervical vertebral bodies.**
- **If the spinal canal is narrowed due to this process it can press on the spinal cord resulting in neurological dysfunction.**
- Myelopathy is thought to occur in around 5-10% of patients who have cervical spondylosis.

### Features

- a variety of motor weakness, sensory loss and bladder/bowel dysfunction may be seen
- neck pain
- wide-based, ataxic or spastic gait

- upper motor neuron weakness in the lower legs - increased reflexes, increased tone and upgoing plantars
- bladder dysfunction e.g., urgency, retention

## Conus medularis syndrome

- Conus medularis syndrome presents with **mixed UMNL** and **LMNL** signs.
- These include bilateral distal weakness with increased tone and hyper-reflexia, fasciculation. Sensory loss is most marked in the perianal region.
- It is much rarer that cauda equina syndrome.
- Cauda equina syndrome is associated with flaccid paralysis.

Spinal cord infarction related to anterior spinal artery disease presents most frequently with sudden onset pain and loss of power and sensation beginning in the thoracic region. The symptoms seen here have slowly built up over a few weeks and affect a more distal spinal cord distribution.
Sacroiliitis would not be associated with neurological deficit.

## Conus Medullaris Syndrome VS Cauda Equina Syndrome

| | Conus Medullaris Syndrome | Cauda Equina Syndrome |
|---|---|---|
| Presentation | Sudden and bilateral | Gradual and may be unilateral leg signs initially |
| Reflexes | Knee jerks preserved, ankle jerks affected | Both knee and ankle jerks affected |
| Radicular pain | Less severe | More severe |
| Sensory | Numbness often localised to perianal area, dissociation can occur, usually bilateral and symmetrical | Numbness often localised to the saddle area, may be asymmetrical and unilateral, sensory loss often dermatomal |
| Motor | Symmetrical, hyperreflexic disal paresis, less marked than cauda equina, may be fasciculations | Areflexic paraplegic, may be asymmetric, more marked than conus medullaris, fasciculations rare, atrophy more common |
| Impotence | Frequent | Often less marked |
| Sphincter dysfunction | Urinary retention and atonic anal sphincter present early in disease (can cause overflow urinary incontinence) | Urinary retention, usually presents later in course of disease |
| Low back pain | More marked | Less marked |

GCS is meaningless unless it is **broken down into its components (E V M)**.

It is important to note that the GCS is unreliable and should not be applied to patients who are inebriated, intubated or who have a therapeutic or traumatic paralysis.

# Degenerative cervical myelopathy

Degenerative cervical myelopathy (DCM) has a number of risk factors, which include smoking due to its effects on the intervertebral discs, genetics and occupation - those exposing patients to high axial loading.

The presentation of DCM is very variable.

Early symptoms are often subtle and can vary in severity day to day, making the disease difficult to detect initially.

However as a progressive condition, worsening, deteriorating or new symptoms should be a warning sign.

### DCM symptoms can include any combination of:

- **Pain (affecting the neck, upper or lower limbs)**
- **Loss of motor function** (loss of digital dexterity, preventing simple tasks such as holding a fork or doing up their shirt buttons, arm or leg weakness/stiffness leading to impaired gait and imbalance
- **Loss of sensory function causing numbness**
- **Loss of autonomic function** (urinary or faecal incontinence and/or impotence) - these can occur and do not necessarily suggest cauda equina syndrome in the absence of other hallmarks of that condition
- **Hoffman's sign:** is a reflex test to assess for cervical myelopathy. It is performed by gently flicking one finger on a patient's hand. A positive test results in reflex twitching of the other fingers on the same hand in response to the flick.

**The most common symptoms at presentation** of DCM are unknown, but in one series 50% of patients were initially incorrectly diagnosed and sometimes treated for carpal tunnel syndrome.

An MRI of the cervical spine is the gold standard test where cervical myelopathy is suspected.

- It may reveal disc degeneration and ligament hypertrophy, with accompanying cord signal change.

All patients with degenerative cervical myelopathy should be urgently referred for assessment by specialist spinal services (neurosurgery or orthopaedic spinal surgery).

- This is due to the importance of early treatment.

- The timing of surgery is important, as any existing spinal cord damage can be permanent.
- Early treatment (within 6 months of diagnosis) offers the best chance of a full recovery but at present, most patients are presenting too late.

In one study, patients averaged over 5 appointments before diagnosis, representing >2 years.

**Currently, decompressive surgery is the only effective treatment.**

- It has been shown to prevent disease progression.

Close observation is an option for mild stable disease,

- but anything progressive or more severe requires surgery to prevent further deterioration.

**Physiotherapy should only** be initiated by specialist services, as manipulation can cause more spinal cord damage.

## Miscellaneous

**Gait disturbance** may occur for a variety of reasons:

- **Sensory** ataxia in B12 deficiency and tabes dorsalis
- **Pyramidal** signs in B12 deficiency and SLE
- **Cerebellar** ataxia in cerebrotendinous xanthomatosis.

## Macroglossia

### Causes

- hypothyroidism
- acromegaly
- amyloidosis
- Duchenne muscular dystrophy
- mucopolysaccharidosis (e.g. Hurler syndrome)

Patients with Down's syndrome are now thought to have apparent macroglossia due to a combination of mid-face hypoplasia and hypotonia

# Internuclear ophthalmoplegia

## Overview

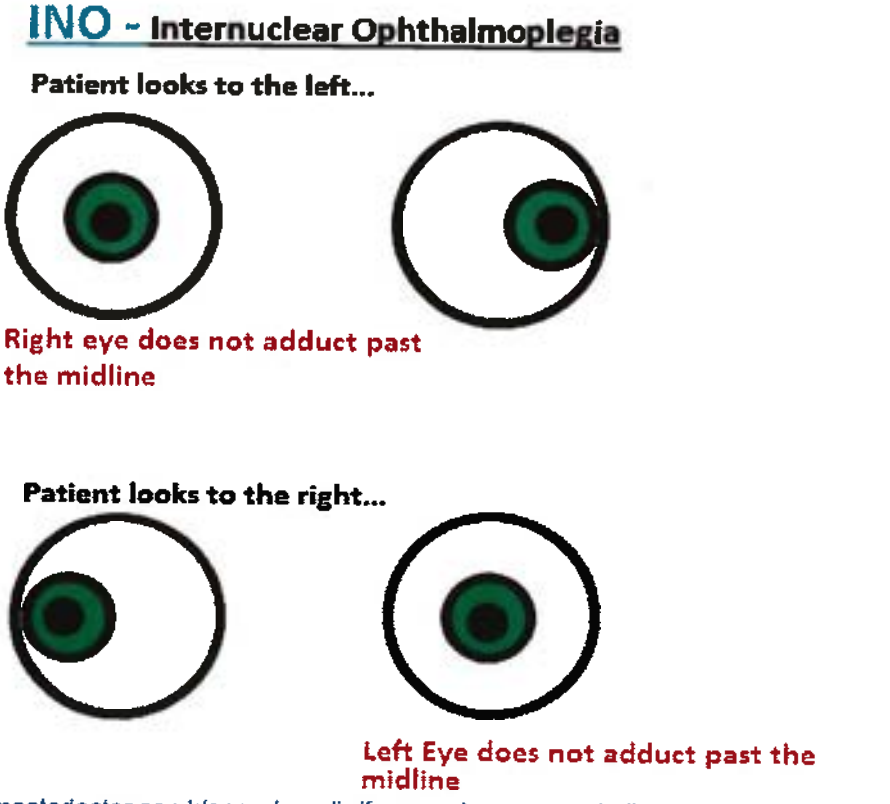
- a cause of horizontal disconjugate eye movement
- due to a lesion in the **medial longitudinal fasciculus** (MLF)
  - controls horizontal eye movements by interconnecting the IIIrd, IVth and VIth cranial nuclei
  - located in the **paramedian area of the midbrain and pons**

## Features

- impaired adduction of the eye on the same side as the lesion
- horizontal nystagmus of the abducting eye on the contralateral side

## Causes

- multiple sclerosis
- vascular disease


INO - Internuclear Ophthalmoplegia
Patient looks to the left...
Right eye does not adduct past the midline
Patient looks to the right...
Left Eye does not adduct past the midline

https://almostadoctor.co.uk/encyclopedia/focussed-exam-cerebellar-and-sensory-ataxia

# Chronic progressive external ophthalmoplegia

- Patients with CPEO typically develop a slowly progressive paresis of extraocular muscles along with bilateral ptosis in the fourth decade of life
- **Often associated with mitochondrial disease** (inherited only from the mother)
- Most common manifestation of mitochondrial myopathy (in two-thirds of all cases).

## Diagnosis

- Lactate in serum and cerebrospinal fluid
- Muscle biopsy → accumulation of enlarged mitochondria **"red ragged fibers"**
- PCR → mutation of mitochondrial DNA.

## Differential diagnosis

- Other causes external ophthalmoplegia must be ruled out, like Graves' disease, myasthenia gravis and glioma .
- Kearns-Sayre syndrome: combination of CPEO with pigmentary retinopathy and onset before age 20 (Ophthalmoplegia + retinitis pigmentosa + AV block)

## Treatments

- surgery can be used to correct ptosis

# Neck lumps

table below gives characteristic exam question features for conditions causing neck lumps:

| Condition | Notes |
|---|---|
| **Reactive lymphadenopathy** | By far the most common cause of neck swellings. There may be a history of local infection or a generalised viral illness |
| **Lymphoma** | Rubbery, painless lymphadenopathy<br>The phenomenon of pain whilst drinking alcohol is very uncommon<br>There may be associated night sweats and splenomegaly |
| **Thyroid swelling** | May be hypo-, eu- or hyperthyroid symptomatically<br>Moves upwards on swallowing |
| **Thyroglossal cyst** | • More common in patients < 20 years old<br>Usually midline, between the isthmus of the thyroid and the hyoid bone<br>• Moves upwards with protrusion of the tongue<br>• May be painful if infected |
| **Pharyngeal pouch** | More common in older men<br>Represents a posteromedial herniation between thyropharyngeus and cricopharyngeus muscles<br>Usually not seen but if large then a midline lump in the neck that gurgles on palpation<br>Typical symptoms are dysphagia, regurgitation, aspiration and chronic cough |
| **Cystic hygroma** | A congenital lymphatic lesion (lymphangioma) typically found in the neck, classically on the left side<br>Most are evident at birth, around 90% present before 2 years of age |
| **Branchial cyst** | An oval, mobile cystic mass that develops between the sternocleidomastoid muscle and the pharynx<br>Develop due to failure of obliteration of the second branchial cleft in embryonic development<br>Usually present in early adulthood |
| **Cervical rib** | More common in adult females<br>Around 10% develop thoracic outlet syndrome |
| **Carotid aneurysm** | Pulsatile lateral neck mass which doesn't move on swallowing |

## Ptosis, Miosis and Mydriasis

| Ptosis | Miosis | Mydriasis |
|---|---|---|
| **Causes of bilateral ptosis:** | **Causes of miosis (small pupil)** | **Causes of dilated pupils include:** |
| - myotonic dystrophy<br>- myasthenia gravis (ptosis is much less common in Lambert Eaton syndrome than myasthenia gravis)<br>- syphilis<br>- congenital | - Horner's syndrome<br>- Argyll-Robertson pupil<br>- senile miosis<br>- pontine haemorrhage<br>- congenital | Holmes-Adie (myotonic) pupil<br>- Third nerve palsy<br>- Drugs, and Poisons (atropine, CO, ethylene glycol). |
| **Causes of unilateral ptosis as bilateral causes plus:** | **Drugs causes** | |
| - third nerve palsy<br>- Horner's | - Opiates<br>- parasympathomimetics: pilocarpine<br>- organophosphate toxicity | |

Ptosis is much more common in myasthenia gravis than Lambert-Eaton syndrome

## Mitochondrial diseases

Whilst most DNA is found in the cell nucleus, a small amount of double-stranded DNA is present in the mitochondria.

It encodes protein components of the respiratory chain and some special types of RNA.

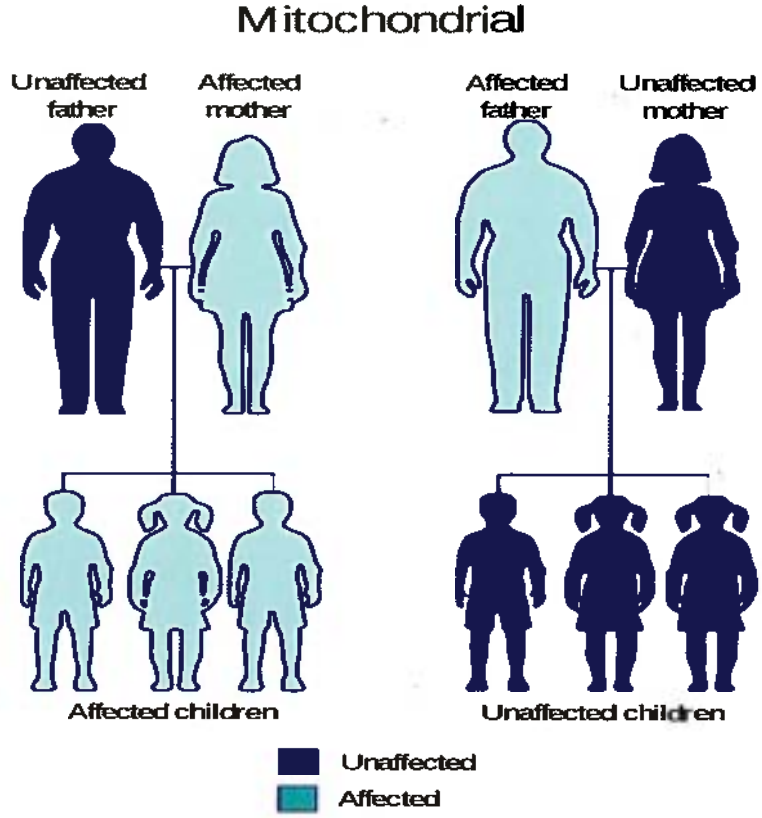
**Mitochondrial inheritance has the following characteristics:**

- Inheritance is **only via the maternal line** as the sperm contributes no cytoplasm to the zygote.
- All children of affected males will not inherit the disease
- All children of affected females will inherit it
- Generally encode rare neurological diseases
- Poor genotype: phenotype correlation - within a tissue or cell there can be different mitochondrial populations - this is known as heteroplasmy.

**Histology:** **Muscle biopsy** classically shows 'red, ragged fibres' due to increased number of mitochondria.

**Examples include:**

- **Leber's optic atrophy**: **bilateral painless visual loss in young boy**.
- **MELAS** syndrome: **M**itochondrial **E**ncephalomyopathy **L**actic **A**cidosis and **S**troke-like episodes.
- **MERRF** syndrome: **M**yoclonus **E**pilepsy with **R**agged-**R**ed **F**ibres.
- **Kearns-Sayre syndrome**: onset in patients **< 20 years old**, external **ophthalmoplegia, retinitis pigmentosa. Bilateral ptosis** may be seen.
- **Sensorineural hearing loss**.




**EX**: A 24-year-old man is investigated for visual loss and is diagnosed as having **Leber's optic atrophy**. So should check **his brothers** and **sister** and sure **his mother** is also affected and is the source of the disease.

# DVLA: neurological disorders

The guidelines below relate to car/motorcycle use unless specifically stated. For obvious reasons, the rules relating to drivers of heavy goods vehicles tend to be much stricter.

## Specific rules:

- **First seizure: 6 months off driving***.
- For patients with **established epilepsy** they must be **fit free for 12 months** before being able to drive.
- **Stroke or TIA: 1 month off** driving
- **Multiple TIAs** over short period of times: **3 months off** driving
- Craniotomy e.g. For meningioma: 1 year off driving**
- Pituitary tumour: craniotomy: 6 months; trans-sphenoidal surgery 'can drive when there is no debarring residual impairment likely to affect safe driving'
- Narcolepsy/cataplexy: cease driving on diagnosis, can restart once 'satisfactory control of symptoms'.
- Chronic neurological disorders e.g. multiple sclerosis, motor neuron disease: DVLA should be informed, complete PK1 form (application for driving licence holder's state of health).
- withdrawawl of epilepsy medication: should not drive whilst anti-epilepsy medication is being withdrawn and for 6 months after the last dose

## Syncope:

- Simple faint: no restriction
- Single episode, explained and treated: 1 month off
- Single episode, unexplained: 6 months off
- Two or more episodes: 12 months off

*Previously rule was 12 months. It is now 6 months off driving if the licence holder has undergone assessment by an appropriate specialist and no relevant abnormality has been identified on investigation, for example EEG and brain scan where indicated.

If the tumour is a benign meningioma and there is no seizure history, licence can be reconsidered 6 months after surgery if remains seizure free.

## DVLA regulations: for seizure and stroke

| Case | Group 1 Car and motorcycle | Group 2 Bus and lorry |
|---|---|---|
| First epileptic seizure / isolate d seizure | no driving for **6 months** | no driving for **5 years** |
| Epilepsy or multiple seizures | no driving for **12 months.** | must remain seizure-free for **10 years** (without epilepsy medication) |
| Dissociative seizures | no driving for **3 months** after event free | no driving for **3 months** after event free |
| Withdrawal of epilepsy medication | no driving for **6 months** after the last dose | must remain seizure-free for **10 years** (without epilepsy medication).(no special considerations for withdrawal) |
| Single TIA, Stroke | no driving for **1 month** | no driving for **1 year** |
| Multiple TIA | no driving for **3 months** | no driving for **1 year** |

## Paraneoplastic syndromes affecting nervous system

### Lambert-Eaton Myasthenic syndrome:

- Associated with small cell lung cancer (also breast and ovarian).
- Antibody directed against pre-synaptic voltage gated calcium channel in the peripheral nervous system.
- Can also occur independently as autoimmune disorder.

### Anti-Hu: (imagine H sticks as 2 lungs or 2 brain hemispheres)

- Associated with small cell lung carcinoma and neuroblastoma.
- **Sensory neuropathy** - may be **painful**
- Cerebellar syndrome
- Encephalomyelitis

### Anti-Yo: (imagine Y as lady's private organs)

- Associated with **ovarian** and **breast** cancer
- **Cerebellar** syndrome

### Anti-GAD antibody:

- Associated with breast, **colorectal** and small cell lung carcinoma
- **Stiff person's syndrome** or **diffuse hypertonia.**

### Anti-Ri:

- Associated with **breast** and small cell lung carcinoma
- **Ocular opsoclonus- myoclonus**

### Purkinje cell antibody

- **peripheral neuropathy in breast cancer**

### GM1 antibodies (Glycolipid ganglioside-monosialic acid) associated with

- Lower motor neuron syndromes
- Amyotrophic lateral sclerosis
- Multiple sclerosis
- Other multifocal neuropathies and
- Systemic lupus erythematosus (SLE) with central nervous system involvement.

**EX**: A 66-year-old woman is investigated for ascites and found to have ovarian cancer. She presents due to 'unsteadiness'. On examination there is evidence of nystagmus and past-pointing. Which one of the following antibodies is most likely to be present? >>> Anti-Yo.

**EX**: A 65-year-old man who is known to have **metastatic colorectal** cancer presents for review. Since last been seen he reports being generally stiff and on examination is noted to have diffuse hypertonia. Which antibodies are most likely to be responsible for this presentation? >>> Anti-GAD.

## HIV: Neurocomplications

| HIV Neuro complications | |
|---|---|
| **Generalised** | **Focal** |
| 1) Encephalitis | 1) Toxoplasmosis |
| 2) Cryptococcus | 2) Lymphoma |
| 3) PML | 3) TB |
| 4) AIDS dementia complex | |

### Generalised neurological disease:

#### Encephalitis

- May be due to CMV or HIV itself
- HSV encephalitis but is relatively rare in the context of HIV
- CT: **oedematous brain**

#### Cryptococcus:

- Most common **fungal** infection of CNS: Cryptococcus neoformans.

- Headache, fever, malaise, nausea/vomiting, seizures, focal neurological deficit.
- Meningitis is typical presentation but may occasionally cause a space occupying lesion
- CSF: **high opening pressure, India ink test positive.**
- CT: **meningeal enhancement, cerebral oedema**

### Management

- **The best management would be intravenous anti-fungal agents, such as amphotericin B and flucytosine.**
- Therapeutic lumber puncture is also advocated to reduce ICP.
- Anti-retroviral (ARV) therapy should not be started immediately, as there is a very high risk of the patient developing IRIS (immune reconstitution inflammatory syndrome). Instead, ARVs should be delayed for several weeks or months after initiating treatment.

## Progressive multifocal leukoencephalopathy (PML):

- **Widespread demyelination**.
- Due to infection of oligodendrocytes by human **papovirus JC virus** (a polyoma **DNA** virus).
- Symptoms, subacute onset: **behavioural changes**, speech, motor, visual impairment, **ataxia, Head tremor, Focal neurology progressing over a period of months to paresis and even coma.**
- Diagnosed by **CSF PCR** for the **JC virus.**
- **CT**: single or multiple lesions, no mass effect, don't usually enhance. **Several areas of Low attenuation diffusely**.
- **MRI** is better - **high-signal demyelinating white matter** lesions are seen.

## AIDS dementia complex:

- Caused by HIV virus itself
- Symptoms: behavioural changes, motor impairment
- CT: **cortical and subcortical atrophy**

## Focal neurological lesions:

### Toxoplasmosis:

- Accounts for around **50%** of **cerebral lesions** in patients with **HIV**.
- Constitutional symptoms, headache, confusion, drowsiness
- CT: usually single or multiple **ring enhancing** lesions, mass effect may be seen
- **Management: sulfadiazine and pyrimethamine**

## Primary CNS lymphoma:

- Accounts for around **30%** of cerebral lesions
- Associated with the **Epstein-Barr virus**
- CT: single or multiple **homogenous** enhancing lesions
- Treatment generally involves steroids (may significantly reduce tumour size), chemotherapy (e.g. methotrexate) + with or without whole brain irradiation. Surgical may be considered for lower grade tumours.

**Differentiating between toxoplasmosis and lymphoma** is a common clinical scenario in HIV patients.

It is clearly important given the vastly different treatment strategies.

| Toxoplasmosis | Lymphoma |
|---|---|
| **Multiple** lesions | Single lesion |
| Ring or nodular **enhancement** | Solid (homogenous) enhancement |
| Thallium SPECT **negative** | Thallium SPECT positive |

## Tuberculosis:

- Much less common than toxoplasmosis or primary CNS lymphoma.
- CT: single enhancing lesion.

**exam: H/O HIV positive, admitted following a seizure + headaches, night sweats and poor appetite. CD4=89 u/l. CT head =Single homogenously-enhancing lesion in the right parietal lobe . What is the most likely diagnosis?**
**>> Primary CNS lymphoma**

**exam:** HIV positive, admitted with confusion, drowsiness and headache. temperature is 37.2°C. CT brain (with contrast): Multiple hypodense regions predominantly in the basal ganglia which show ring enhancement. Minimal surrounding oedema. No mass effect. What is the most likely diagnosis?
**>> Cerebral toxoplasmosis** (HIV - multiple ring enhancing lesions = toxoplasmosis)

# Pituitary tumours

## Hormones secreted:

- **Prolactin- 35%**
- No obvious hormone, 'non-functioning', 'chromophobe' - 30%
- Growth hormone - 20%
- Prolactin and growth hormone - 7%
- ACTH - 7%
- Others: TSH, LH, FSH - 1%

**NB: Prolactinomas** are unusual as **medical** therapy is **first** line, **even if visual** field defects are present.

The main indications for surgery are tumours resistant to dopamine agonists.

**Prolactinoma** management >> **Medical** therapy (**dopamine agonist**) is almost always **first-line**, even if visual field defects are present.

# NEUROLOGICAL PHARMACOLOGY

## Phenytoin (Epanutin ®)

Phenytoin is used to in the management of seizures.

**Mechanism of action: Na channel blocker**, decreasing the sodium influx into neurons which in turn decreases excitability.

**Adverse effects:**

Phenytoin is associated with a large number of adverse effects.

These may be divided into acute, chronic, idiosyncratic and teratogenic.

**1) Acute:**

- Initially: **Cerebellum syndrome**: **Ataxia, Dizziness, Diplopia, Nystagmus, Chorea, Slurred speech.**
- Later: confusion, seizures.

Phenytoin toxicity typically gives rise to a cerebellar-like syndrome

**2) Chronic:**

- Common: **gingival hyperplasia** (secondary to increased expression of platelet derived growth factor, PDGF), **hirsutism (شعر), acne, coarsening of facial features**, drowsiness.
- **Megaloblastic anaemia** (secondary to altered **Folate** metabolism).
- **Pancytopenia**
- **Peripheral neuropathy.**
- Enhanced vitamin D metabolism causing **osteomalacia**.
- **Lymphadenopathy, Pseudolymphoma or, rarely, malignant lymphoma and mycosis-fungoides-like lesions.**

R/ Epanutin + Folic acid + Vit B complex + Pregabalin+ Calcium with Vit D

### 3) Idiosyncratic:

- Fever
- **Rashes**, up to severe reactions as toxic epidermal necrolysis (**TEN**)
- Hepatitis
- Dupuytren's contracture (although not listed in the BNF).
- Aplastic anaemia
- Drug-induced lupus

### 4) Teratogenic:

- Associated with cleft palate and congenital heart disease.

**Usage of phenytoin in renal impairment:**
Patient with renal failure, a state in which **drugs** that are usually **highly protein bound**, such as phenytoin, sodium valproate and warfarin. **Lose some of their affinity for protein binding**. This results in **increased availability of free drug** at any given dose, which then **increases the risk of toxicity.**

**So you will find signs of phenytoin toxicity but with normal Phenytoin levels in blood by the lab**

Because **laboratory** assays for phenytoin usually measure **total** drug concentration, this gives a degree of **false reassurance**.

So in patients with renal failure, **dose reduction of phenytoin** is required.

## Sodium valproate (Depakin®)

Offer sodium valproate as first-line monotherapy for generalised tonic-clonic seizures in:

- boys and men
- girls aged under 10 years and who are unlikely to need treatment when they are old enough to have children
- women who are unable to have children.

It works by **increasing ↑GABA activity.**

### Adverse effects:

- GIT: anorexia, nausea, vomiting
- **PCOS like picture**: weight gain, acne, hair loss: so ↓ use in **females.**
- Highly **teratogenic**: neural tube defects.
- **Alopecia (in 12 % of cases)**: regrowth may be curly

- Ataxia
- **Tremor**
- **Hepatitis**
- **Pancreatitis**
- Thrombocytopenia
- Hyponatraemia
- Enzyme **Inhibitor** P450 enzyme system

**Na valproate** SE: nausea, ↑ appetite, ↑ weight gain, **Alopecia** (أصلع), Ataxia, Hepatitis, Pancreatitis and Teratogenic.
Sodium valproate can occasionally have an **idiosyncratic** response leading to **severe** or even **fatal hepatic toxicity**.

Offer lamotrigine or levetiracetam as first-line monotherapy for generalized tonic-clonic seizures in women and girls able to have children (including young girls who are likely to need treatment when they are old enough to have children). If the first choice is unsuccessful, offer the other of these options.

**If monotherapy is unsuccessful in people with generalized tonic-clonic seizures, consider 1 of the following first-line add-on treatment options:** • **clobazam** • **lamotrigine** • **levetiracetam** • **perampanel** • **sodium valproate**, except in women and girls able to have children Epilepsies in children, young people and adults • topiramate.
**If the first choice is unsuccessful, consider the other first-line add-on options.**

If first-line add-on treatments tried are unsuccessful in people with generalized tonic-clonic seizures, consider 1 of the following second-line add-on treatment options: • **brivaracetam** • **lacosamide** • **phenobarbital** • **primidone** • **zonisamide**. If the first choice is unsuccessful, consider the other second-line add-on options.

## Carbamazepine

Carbamazepine is chemically similar to the tricyclic antidepressant drugs. It is most commonly used in the treatment of epilepsy, particularly partial seizures, where carbamazepine remains a first-line medication. Other uses include

- trigeminal neuralgia
- bipolar disorder

Carbamazepine is known to exhibit autoinduction, hence when patients start carbamazepine they may see a return of seizures after 3-4 weeks of treatment.

### Mechanism of action:

- **binds to sodium channels increases their refractory period**
  Adverse effects
- **P450 enzyme inducer**
- **dizziness and ataxia**
- **drowsiness**
- **headache**
- visual disturbances (especially **diplopia)**
- **Steven-Johnson syndrome**
- **leucopenia and agranulocytosis**
- **hyponatraemia** secondary to syndrome of inappropriate ADH secretion
- **hepatotoxicity, Toxic Epidermal Necrolysis (TEN)**

## 5-HT3 antagonists

5-HT3 antagonists are antiemetics used mainly in the management of chemotherapy-related nausea. They mainly act in the chemoreceptor trigger zone area of the medulla oblongata.

### Examples

- ondansetron
- palonosetron
  - second-generation 5-HT3 antagonist
  - main advantage is reduced effect on the QT interval

### Adverse effects

- prolonged QT interval
- constipation is common.

### Baclofen

Baclofen is used to treat muscle spasticity in conditions such as multiple sclerosis, cerebral palsy and spinal cord injuries.

### Mechanism of action

- agonist of GABA receptors
- acts in the central nervous system (brain and spinal cord)

## Ethosuximide

Ethosuximide is an antiepileptic that is particularly indicated in patients with absence seizures

### Mechanism of action

- blocks T-type calcium channels in thalamic neurons

## Topiramate

Topiramate was developed as an antiepileptic and is used alone or as adjunctive treatment in generalised tonic-clonic seizures.

**There appear to be multiple mechanisms of action:**

- blocks voltage-gated Na+ channels
- increases GABA action
- carbonic anhydrase inhibition: this results in a decrease in urinary citrate excretion and formation of alkaline urine that favours the creation of calcium phosphate stone

Topiramate is an inducer of the P450 enzyme CYP3A4. This may result in hormonal contraception being less effective. As a result, the Faculty of Sexual and Reproductive Health (FSRH) suggests the following for patients taking topiramate:

- combined oral contraceptive pill and progestogen-only pill: UKMEC 3 (disadvantages outweigh advantages):
- implant: UKMEC 2 (advantages generally outweigh the disadvantages)

The injection (Depo-Provera) and intrauterine system are not affected by topiramate.

### Adverse effects of topiramate include:

- reduced appetite and weight loss
- dizziness
- paraesthesia
- lethargy and poor concentration
- rare but important: acute myopia and **secondary angle-closure glaucoma**

Topiramate is associated with a risk of foetal malformations.

# Triptans

Triptans are specific **5-HT1B and 5-HT1D agonists** used in the acute treatment of migraine. They are generally used first-line in combination therapy with an NSAID or paracetamol.

## Prescribing points

- should be taken as soon as possible after the onset of headache, rather than at onset of aura
- oral, orodispersible, nasal spray and subcutaneous injections are available

## Adverse effects

- 'triptan sensations' - tingling, heat, tightness (e.g. throat and chest), heaviness, pressure

## Contraindications

- patients with a history of, or significant risk factors for, **ischaemic heart disease or cerebrovascular disease**

# Psychiatry

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# Lithium

Lithium is mood stabilizing drug used most commonly prophylactically in bipolar disorder but also as an adjunct in refractory depression. It has a very narrow therapeutic range (0.4-1.0 mmol/L) and a long plasma half-life being excreted primarily by the kidneys.

## Mechanism of action - not fully understood, two theories:

- interferes with inositol triphosphate formation
- interferes with cAMP formation

## Adverse effects

- nausea/vomiting, diarrhoea
- **fine tremor**
- **nephrotoxicity:** polyuria, secondary to nephrogenic **diabetes insipidus**
- thyroid enlargement, may lead to **hypothyroidism**
- ECG: T wave flattening/inversion
- **weight gain**
- idiopathic **intracranial hypertension**
- leukocytosis
- hyperparathyroidism and resultant hypercalcemia

## Monitoring of patients on lithium therapy

- inadequate monitoring of patients taking lithium is common - NICE and the National Patient Safety Agency (NPSA) have issued guidance to try and address this. As a result it is often an exam hot topic
- when checking lithium levels, the sample should be taken 12 hours post-dose
- after starting lithium levels should be performed weekly and after each dose change until concentrations are stable
- once established, lithium blood level should 'normally' be checked every 3 months
- after a change in dose, lithium levels should be taken a week later and weekly until the levels are stable.
- thyroid and renal function should be checked every 6 months
- patients should be issued with an information booklet, alert card and record book

# Antipsychotics

- Antipsychotics are a group of drugs used in the management of schizophrenia and other forms of psychosis, mania and agitation.
- They are usually divided into typical and atypical antipsychotics.
- The atypical antipsychotics were developed due to the problematic extrapyramidal side-effects which are associated with the first generation of typical antipsychotics.

| | Typical antipsychotics | Atypical antipsychotics |
|---|---|---|
| **Mechanism of action** | Dopamine D2 receptor antagonists, blocking dopaminergic transmission in the mesolimbic pathways | Act on a variety of receptors (D2, D3, D4, 5-HT) |
| **Adverse effects** | Extrapyramidal side-effects and hyperprolactinaemia common | Extrapyramidal side-effects and hyperprolactinaemia less common<br>Metabolic effects |
| **Examples** | Haloperidol<br>Chlopromazine | Clozapine<br>Risperidone<br>Olanzapine |

**The rest of this section will focus on typical antipsychotics, with atypical antipsychotics covered elsewhere.**

## Extrapyramidal side-effects (EPSEs)

- Parkinsonism
- acute dystonia
  - sustained muscle contraction (e.g. torticollis, oculogyric crisis)
  - may be **managed with procyclidine**
- **akathisia (severe restlessness)**
- tardive dyskinesia (late onset of choreoathetoid movements, abnormal, involuntary, may occur in 40% of patients, may be irreversible, most common is chewing and pouting of jaw).

**The Medicines and Healthcare products Regulatory Agency has issued specific warnings when antipsychotics are used in elderly patients:**

- increased risk of stroke
- increased risk of venous thromboembolism

## Other side-effects

- antimuscarinic: dry mouth, blurred vision, urinary retention, constipation
- sedation, weight gain
- raised prolactin
  - may result in galactorrhoea
  - due to inhibition of the dopaminergic tuberoinfundibular pathway
- impaired glucose tolerance
- neuroleptic malignant syndrome: pyrexia, muscle stiffness
- reduced seizure threshold (greater with atypicals)
- prolonged QT interval (particularly haloperidol)

### Examples of atypical antipsychotics

- clozapine
- olanzapine: higher risk of dyslipidemia and obesity
- risperidone
- quetiapine
- amisulpride
- aripiprazole: generally good side-effect profile, particularly for prolactin elevation

## Clozapine

Clozapine, one of the first atypical agents to be developed, carries a significant risk of agranulocytosis and full blood count monitoring is therefore essential during treatment.
For this reason, clozapine should only be used in patients resistant to other antipsychotic medication. The BNF states:

Clozapine should be introduced if schizophrenia is not controlled despite the sequential use of two or more antipsychotic drugs (one of which should be a second-generation antipsychotic drug), each for at least 6–8 weeks.

### Adverse effects of clozapine

- agranulocytosis (1%), neutropaenia (3%)
- reduced seizure threshold - can induce seizures in up to 3% of patients
- constipation
- myocarditis: a baseline ECG should be taken before starting treatment
- hypersalivation

Dose adjustment of clozapine might be necessary if smoking is started or stopped during treatment.

# Neuroleptic malignant syndrome (NMS)

- It is a **rare** but **dangerous** condition seen in patients taking **antipsychotic** medication (e.g. Olanzapine haloperidol, chlorpromazine and Citalopram).
- It carries a mortality of up to 10% and can also occur with **atypical antipsychotics**.
- It may also occur with **dopaminergic drugs (such as levodopa)** for **Parkinson's** disease, usually when the **drug is suddenly stopped** or **the dose reduced**.
- It is thought to arise from blockage of dopamine receptors or decrease in availability of dopamine (**↓ Dopamine**).
- **Primary diagnostic features are altered conscious level, autonomic instability and muscular rigidity with raised CPK**
- It can occur **within hours** of initiating drug therapy, but typically takes about **1 week**.
- The mortality is between 10-20%.

## Features:

- More common in **young male** patients
- **Onset usually in first 10 days of treatment or after increasing dose of** antipsychotic.
- **Pyrexia**
- **Altered mental status**
- **Muscle rigidity** (sometimes with dysphagia and dysarthria).
- **Extrapyramidal signs, tremors, catatonia, muteness.**
- **Tachycardia**
- **Autonomic dysfunction.**
- A raised **CPK** & **AST** is present in most cases.
- A **leucocytosis** may also be seen.
- **Renal failure** may occur secondary to **rhabdomyolysis**
- **Metabolic acidosis.**
- **DIC.**

## Management:

- **Stop** antipsychotic.
- **IV fluids** to prevent renal failure.
- **Bromocriptine**, **Dopamine agonist**.
- **Dantrolene IV** was formerly recommended as monotherapy, case series suggests that when it is used in the absence of Bromocriptine, mortality may actually be increased.

**Dantrolene** is thought to work by decreasing excitation-contraction coupling in skeletal muscle by binding to the ryanodine receptor, and decreasing the release of calcium from the sarcoplasmic reticulum.

EX: A 35-year-old man with a history of schizophrenia is brought to the ED by worried friends due to drowsiness. On examination he is generally rigid. >>> A diagnosis of neuroleptic malignant syndrome should be suspected.

## Serotonin syndrome

- **Myoclonus is the distinguishing feature of serotonin syndrome (found only in serotonin syndrome).**
- **Occur** in those taking therapeutic doses of SSRIs, as part of **drug-drug interaction** (e.g. the addition of: ondansetron, amphetamine, cocaine, meperidine (Pethidine), dextromethorphan, fentanyl, buspiron, ergot alkaloids, lithium, L-dopa, LSD, St. John's Wort), or following intentional **self-poisoning** with SSRI.

**Symptoms can occur within days and can last months following withdrawal and then disappear.**

1) **Psychiatric**:
   - Increased mood change
   - Confusion, agitation, hypomania, anxiety, and
   - Difficulty sleeping
   - **Sweating**
2) **Neurological**:
   - **Coma**
   - **Hyperthermia**, **hyperreflexia**, myoclonus **ataxia**, **unsteadiness**
   - **Restlessness, hallucination, up to seizures.**
   - **Paraesthesia**
   - **Mydriasis**
   - Headache, dizziness
3) **GIT symptoms**: pain, cramping, **nausea**, **vomiting**, **diarrhoea**.
4) **Hypertension, tachycardia, pyrexia**
5) **DIC** (↓ PLT, ↑PT, ↑ PTT, ↓Fibrinogen).

It is thought that shorter acting SSRIs, when discontinued or when the dosage is lowered, produce **an "anticholinergic rebound,"** interrupting the production of the acetylcholine.

## Treatment

- **stopping any serotonergic agents**
- **using benzodiazepines for agitation**
- **consideration of use of serotonin antagonists such as cyproheptadine if there is severe autonomic disturbance.**

| Neuroleptic malignant syndrome | Serotonin syndrome |
|---|---|
| • develops over days to weeks. | • develops over 24 hours. |
| • characterized by sluggish neuromuscular responses (rigidity, bradyreflexia). | • characterized by neuromuscular hyperreactivity (**tremor, hyperreflexia, myoclonus**). |
| • resolution typically requires an average of nine days. | • resolution typically requires less than 24 hours. |

**Management of depression in elderly with Alzheimer's**

- **citalopram is the best treatment**
  - Although citalopram may have minor effects on cognition, it has been shown in patients with Alzheimer's to impact positively on patient mood and wellbeing and is associated with a significant improvement in agitation and care giver distress.
  - Dose limitation to 20 mg is generally recommended in the elderly because of a risk of QT prolongation.
- Fluoxetine and sertraline have no significant positive effect on mood in patients with Alzheimer's disease, whilst valproate is of value as a mood stabilizer outside the context of Alzheimer's, it is of little value in patients with the condition.

while not as selective as the SSRIs, drugs of abuse such as cocaine, fenfluramine, and (3,4-meth lenedioxmetham hetamine **MDMA** or ecstasy) are **inhibitors of serotonin uptake.**

## Selective serotonin reuptake inhibitors

**Selective serotonin reuptake inhibitors (SSRIs) are considered first-line treatment for the majority of patients with depression.**

- citalopram (although see below re: QT interval) and fluoxetine are currently the preferred SSRIs
- **sertraline is useful post myocardial infarction** as there is more evidence for its safe use in this situation than other antidepressants
- SSRIs should be used with caution in children and adolescents. Fluoxetine is the drug of choice when an antidepressant is indicated

## Adverse effects

- gastrointestinal symptoms are the most common side-effect
- there is an increased risk of gastrointestinal bleeding in patients taking SSRIs. A proton pump inhibitor should be prescribed if a patient is also taking a NSAID
- patients should be counselled to be vigilant for increased anxiety and agitation after starting a SSRI
- fluoxetine and paroxetine have a higher propensity for drug interactions

## Citalopram and the QT interval

- the Medicines and Healthcare products Regulatory Agency (MHRA) released a warning on the use of citalopram in 2011
- it advised that citalopram and escitalopram are associated with dose-dependent QT interval prolongation and should not be used in those with: congenital long QT syndrome; known pre-existing QT interval prolongation; or in combination with other medicines that prolong the QT interval
- the maximum daily dose is now 40 mg for adults; 20 mg for patients older than 65 years; and 20 mg for those with hepatic impairment

## Interactions

- **NSAIDs**: NICE guidelines advise 'do not normally offer SSRIs', but if given co-prescribe a proton pump inhibitor
- warfarin / heparin: NICE guidelines recommend avoiding SSRIs and considering mirtazapine
- aspirin: see above
- triptans - increased risk of serotonin syndrome
- monoamine oxidase inhibitors (MAOIs) - increased risk of serotonin syndrome

Following the initiation of antidepressant therapy patients should normally be reviewed by a doctor after 2 weeks.

For patients under the age of 30 years or at increased risk of suicide they should be reviewed after 1 week.

If a patient makes a good response to antidepressant therapy they should continue on treatment for at least 6 months after remission as this reduces the risk of relapse.

When stopping a SSRI the dose should be gradually reduced over a 4 week period (this is not necessary with fluoxetine). **Paroxetine has a higher incidence of discontinuation symptoms.**

### Discontinuation symptoms

- increased mood change
- restlessness
- difficulty sleeping
- unsteadiness
- sweating
- gastrointestinal symptoms: pain, cramping, diarrhoea, vomiting
- paraesthesia

### SSRIs and pregnancy

- BNF says to weigh up benefits and risk when deciding whether to use in pregnancy.
- Use during the first trimester gives a small increased risk of congenital heart defects
- Use during the third trimester can result in persistent pulmonary hypertension of the newborn
- Paroxetine has an increased risk of congenital malformations, particularly in the first trimester

## Serotonin and noradrenaline reuptake inhibitors

Serotonin and noradrenaline reuptake inhibitor (SNRI's) are a class of relatively new antidepressants.
Inhibiting the reuptake increases the concentrations of serotonin and noradrenaline in the synaptic cleft leading to the effects.
Examples include **venlafaxine and duloxetine**.
They are used to treat major depressive disorders, generalised anxiety disorder, social anxiety disorder and panic disorder and menopausal symptoms.

## Monoamine oxidase inhibitors

### Overview

- serotonin and noradrenaline are metabolised by monoamine oxidase in the presynaptic cell

### Non-selective monoamine oxidase inhibitors

- e.g. tranylcypromine, phenelzine
- used in the treatment of atypical depression (e.g. hyperphagia) and other psychiatric disorder
- not used frequently due to side-effects

### Adverse effects of non-selective monoamine oxidase inhibitors

- hypertensive reactions with tyramine containing foods e.g. cheese, pickled herring, Bovril, Oxo, Marmite, broad beans
- anticholinergic effects

## Tricyclic antidepressants

Tricyclic antidepressants (TCAs) are used less commonly now for depression due to their side-effects and toxicity in overdose.
They are however used widely in the treatment of neuropathic pain, where smaller doses are typically required.

### Common side-effects

- drowsiness
- dry mouth
- blurred vision
- constipation
- urinary retention
- lengthening of QT interval

### Choice of tricyclic

- low-dose amitriptyline is commonly used in the management of neuropathic pain and the prophylaxis of headache (both tension and migraine)
- lofepramine has a lower incidence of toxicity in overdose
- **amitriptyline and dosulepin (dothiepin) are considered the most dangerous in overdose**

| More sedative | Less sedative |
|---|---|
| Amitriptyline<br>Clomipramine<br>**Dosulepin**<br>Trazodone | Imipramine<br>**Lofepramine**<br>Nortriptyline |

*trazodone is technically a 'tricyclic-related antidepressant'

### Tricyclic overdose

- Overdose of tricyclic antidepressants (TCA) is a common presentation to emergency departments.
- **Amitriptyline (Tryptizole ®)** and **Dosulepin (Dothiepin) (Prothiadine 75mg)** are particularly dangerous in overdose.
- Early features relate to **anticholinergic properties**: dry mouth, dilated pupils, agitation, sinus tachycardia, blurred vision.

## Features of severe poisoning include:

- **Anticholinergic** effects: mydriasis, dry skin, dry mouth, urinary retention, constipation, confusion.
- **Confusion, seizures and coma**
- **Metabolic acidosis**
- **Arrhythmias** & **ECG** changes include:
  - Sinus tachycardia
  - **Widening of QRS**
  - **Prolongation of QT interval >> VT**

Widening of **QRS > 100ms** is associated with an increased risk of **seizures** whilst **QRS > 160ms** is associated with **ventricular arrhythmias**.

## Management:

- **IV (NaHCO3) 50 mmol**: may reduce the risk of seizures and arrhythmias in severe toxicity.
- Treatment of Arrhythmias:
  - **Lignocaine:** it increases the electrical stimulation threshold of the ventricle, suppressing the automaticity of conduction and terminating VT, it should be emphasized that **correction of acidosis is the first line in management** of tricyclic induced **arrhythmias**.
  - Class 1A antiarrhythmic (e.g. Quinidine) and class IC (e.g. Flecainide) are contraindicated as they prolong depolarisation. Class III (as amiodarone) should also be avoided as they prolong the QT interval.
- Dialysis is ineffective in removing TCA.

**EX.** Pt with **TCA overdose** (e.g. amitriptyline) with marked **tachycardia** >>> the **first** step would be to >>> obtain an **ECG**. If changes such as **QRS widening** are seen then **IV bicarbonate** should be given.
An ECG would immediately indicate if there is a risk of significant TCA toxicity by showing a wide QRS complex or abnormal axis deviation.

TCA overdose >>> give **IV Na bicarbonate (NaHCO3)**

**Amiodarone** is best **avoided** in TCA overdose as it may increase the risk of torsade due to QT prolongation.

**NB**: Arrhythmias following tricyclic overdose are difficult to treat as many commonly used anti-arrhythmic are contraindicated. **The use of sodium bicarbonate has been shown to be effective, even in patients who are not acidotic.** This is a rare occasion where NaHCO3 IV is recommended as first line therapy, here for VT/QRS widening in TCA poisoning. It provides exogenous Na to overcome the competitive fast Na channel blockade produced by TCA, and produces an alkalaemia (or reverses acidaemia) that mitigates the fast Na channel blockade by the TCA ingested.

## Atypical antidepressants

### Mirtazapine

#### Mechanism of action

- aradrenergic antagonist >> ↑ serotonin and norepinephrine release
- **5-HT2 and 5-HT$_3$ receptor antagonist >> ↑ effect of serotonin on free 5-HT1 receptor >> likely responsible for antidepressant effects**
- H1 antagonist

#### Indications

- major depressive disorder, especially in underweight and insomniac patients

#### Side effects

- ↑ appetite and weight gain
- Sedation (due to H1 antagonism)

#### Contraindications

- risk of serotonin syndrome if given concomitantly within 14 days of MAOIs, linezolid, or methylene blue use

### Bupropion

#### Mechanism of action

- not fully understood, but thought to **increase dopamine and norepinephrine levels via reuptake inhibition**

#### Indications

- **Smoking cessation:**
  - used in conjunction with counseling and nicotine replacement
- Major depressive disorder
- Depressive disorders with seasonal pattern

#### Side effects

- **Reduction of seizure threshold**
- Tachycardia, palpitations, agitation

- Weight loss
- Neuropsychiatric symptoms (including depression, mania, psychosis, and paranoia)

### Contraindications

- Patients with ↑ risk for seizure (epilepsy, anorexia/bulimia, alcohol or benzodiazepine withdrawal, etc.)
- Risk of serotonin syndrome if given concomitantly within 14 days of MAOIs, linezolid, or methylene blue use

### Additional information

- Bupropion has **no sexual side effects**, which makes it a viable alternative to SSRIs or SSNRIs for patients who experience sexual dysfunction.

## Benzodiazepines

Benzodiazepines enhance the effect of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) by increasing the **frequency** of chloride channels. They therefore are used for a variety of purposes:

- sedation
- hypnotic
- anxiolytic
- anticonvulsant
- muscle relaxant

Patients commonly develop a tolerance and dependence to benzodiazepines and care should therefore be exercised on prescribing these drugs.
The Committee on Safety of Medicines advises that benzodiazepines are only prescribed for a short period of time (2-4 weeks).

The BNF gives advice on how to withdraw a benzodiazepine.
The dose should be withdrawn in steps of about 1/8 (range 1/10 to 1/4) of the daily dose every fortnight.
A suggested protocol for patients experiencing difficulty is given:

- switch patients to the equivalent dose of diazepam
- reduce dose of diazepam every 2-3 weeks in steps of 2 or 2.5 mg
- time needed for withdrawal can vary from 4 weeks to a year or more

If patients withdraw too quickly from benzodiazepines they may experience benzodiazepine withdrawal syndrome, a condition very similar to alcohol withdrawal syndrome. This may occur up to 3 weeks after stopping a long-acting drug. Features include:

- insomnia
- irritability
- anxiety

- tremor
- loss of appetite
- tinnitus
- perspiration
- perceptual disturbances
- seizures

**$GABA_A$ drugs**

- benzodiazipines increase the **frequency** of chloride channels
- barbiturates increase the **duration** of chloride channel opening

**Fre**quently **Ben**d - **Dur**ing **Barb**eque
...or...
Barbi**durat**es increase **durat**ion & **Fren**dodiazepines increase **fre**quency

## Schizophrenia

The strongest risk factor for developing a psychotic disorder (including schizophrenia) is **family history**.
Having a parent with schizophrenia leads to a relative risk (RR) of 7.5.

**Risk of developing schizophrenia**

- **monozygotic twin has schizophrenia = 50%**
- parent has schizophrenia = 10-15%
- sibling has schizophrenia = 10%
- no relatives with schizophrenia = 1%

**Other selected risk factors for psychotic disorders include:**

- Black Caribbean ethnicity - RR 5.4
- Migration - RR 2.9
- Urban environment- RR 2.4
- Cannabis use - RR 1.4

### Features

**Schneider's first rank symptoms may be divided into auditory hallucinations, thought disorders, passivity phenomena and delusional perceptions:**

**Auditory hallucinations of a specific type:**

- two or more voices discussing the patient in the third person
- thought echo
- voices commenting on the patient's behaviour

**Thought disorder:**

- thought insertion
- thought withdrawal
- thought broadcasting

### Passivity phenomena:

- bodily sensations being controlled by external influence
- actions/impulses/feelings - experiences which are imposed on the individual or influenced by others

### Delusional perceptions

- a two stage process) where first a normal object is perceived then secondly there is a sudden intense delusional insight into the objects meaning for the patient e.g. 'The traffic light is green therefore I am the King'.

### Other features of schizophrenia include

- impaired insight
- incongruity/blunting of affect (inappropriate emotion for circumstances)
- decreased speech
- neologisms: made-up words
- catatonia
- **Concrete thinking where a patient cannot use abstraction to understand the meaning of a sentence.** It is more common in schizophrenia.
- negative symptoms: incongruity/blunting of affect, anhedonia (inability to derive pleasure), alogia (poverty of speech), avolition (poor motivation)

*Occasionally referred to as thought alienation

### NICE published guidelines on the management of schizophrenia.

**Key points:**

- oral atypical antipsychotics are first-line
- cognitive behavioural therapy should be offered to all patients
- close attention should be paid to cardiovascular risk-factor modification due to the high rates of cardiovascular disease in schizophrenic patients (linked to antipsychotic medication and high smoking rates)

## Prognostic indicators

### Factors associated with poor prognosis

- strong family history
- gradual onset
- low IQ
- prodromal phase of social withdrawal
- lack of obvious precipitant

## Acute stress disorder

Acute stress disorder is **defined as** an acute stress reaction that occurs in the first 4 weeks after a person has been exposed to a traumatic event (threatened death, serious injury e.g., road traffic accident, sexual assault etc.). This is in contrast to post-traumatic stress disorder (PTSD) which is diagnosed after 4 weeks.

### Features include:

- intrusive thoughts e.g. flashbacks, nightmares
- dissociation e.g. 'being in a daze', time slowing
- negative mood
- avoidance
- arousal e.g. hypervigilance, sleep disturbance

### Management

- **trauma-focused cognitive-behavioural therapy (CBT)** is usually used first-line
- benzodiazepines
  - sometimes used for acute symptoms e.g. agitation, sleep disturbance
  - should only be used with caution due to addictive potential and concerns that they may be detrimental to adaptation

## Obsessive-compulsive disorder

Obsessive-compulsive disorder (OCD) is characterized by the presence of either obsessions or compulsions, but commonly both.
The symptoms can cause significant functional impairment and/ or distress.

It is associated with rituals, fears (for example, hurting others but rarely carried out), thoughts abhorrent to the patient and ruminations. **Patients maintain good insight** and often find the illness distressing (which can lead to depression).
It typically starts in **early adult life** and has equal sex incidence.

**An obsession is defined as: an unwanted intrusive thought, image or urge that repeatedly enters the person's mind.**
**Compulsions are: repetitive behavior or mental acts that the person feels driven to perform.**

**A compulsion can either be overt and observable by others, such as checking that a door is locked, or a covert mental act that cannot be observed, such as repeating a certain phrase in one's mind.**

It is thought that 1 to 2% of the population have OCD, although some studies have estimated 2 to 3%.

## The etiology is multifactorial but possible factors include:

- genetic
- psychological trauma
- pediatric autoimmune neuropsychiatric disorder associated with streptococcal infections (PANDAS)

## Associations

- depression (30%)
- schizophrenia (3%)
- Sydenham's chorea
- Tourette's syndrome
- anorexia nervosa

## Management

### If functional impairment is mild

- low-intensity psychological treatments: cognitive behavioral therapy (CBT) including exposure and response prevention (ERP)
- If this is insufficient or can't engage in psychological therapy, then offer choice of either a course of an SSRI or more intensive CBT (including ERP)

### If moderate functional impairment

- offer a choice of either a course of an SSRI (any SSRI for OCD but fluoxetine specifically for body dysmorphic disorder) or more intensive CBT (including ERP)

### If severe functional impairment

- offer combined treatment with an SSRI and CBT (including ERP)

## Notes on treatments

- ERP is a psychological method which involves exposing a patient to an anxiety provoking situation (e.g. for someone with OCD, having dirty hands) and then stopping them engaging in their usual safety behaviour (e.g. washing their hands). This helps them confront their anxiety and the habituation leads to the eventual extinction of the response
- if treatment with SSRI is effective then continue for at least 12 months to prevent relapse and allow time for improvement
- If SSRI ineffective or not tolerated try either another SSRI

## Othello's syndrome

Othello's syndrome is pathological jealousy where a person is convinced their partner is cheating on them without any real proof.
This is accompanied by socially unacceptable behaviour linked to these claims.

## Sleep paralysis

Sleep paralysis is a common condition characterized by transient paralysis of skeletal muscles which occurs when awakening from sleep or less often while falling asleep.
It is thought to be related to the paralysis that occurs as a natural part of REM (rapid eye movement) sleep.
Sleep paralysis is recognised in a wide variety of cultures

### Features

- paralysis - this occurs after waking up or shortly before falling asleep
- hallucinations - images or speaking that appear during the paralysis

### Management

- if troublesome clonazepam may be used

- **EX**: A 23-year-old man presents as he is concerned about a number of recent episodes related to sleep. He finds when he wakes up and less often when he is falling asleep he is 'paralysed' and unable to move. This sometimes associated with what the patient describes as 'hallucinations' such as seeing another person in the room.
- **Rapid eye movement (REM) sleep behaviour disorder**, is a parasomnia manifested by **vivid dreams** associated with simple or complex motor behaviour during REM sleep. Polysomnography demonstrates increased electromyographic tone and dream enactment, often associated with the **violent** re-enacting of dreams and occuring when the normal atonicity of REM sleep is lost.
- There is an association with the later development of movement disorders and these can be predicted by a number of years.
- **Parkinson's disease** in increasingly linked with REM sleep behaviour disorder.

- Making the situation safe is paramount but treatment with **clonazepam** is the intervention of choice. Counselling can also play a role

## Cotard syndrome

Cotard syndrome is a rare mental disorder where the affected patient **believes that they (or in some cases just a part of their body) is either dead or non-existent.**
This delusion is often difficult to treat and can result in significant problems due to patients stopping eating or drinking as they deem it not necessary.

Cotard syndrome is associated with severe depression and psychotic disorders.

## Unexplained symptoms

**There are a wide variety of psychiatric terms for patients who have symptoms for which no organic cause can be found:**

**Unexplained symptoms:**
- **S**omatisation = **S**ymptoms
- Hypo**C**hondria = **C**ancer

### Somatisation disorder:

- Multiple physical **SYMPTOMS** present for **at least 2 years** and can be associated with **multiple medical admissions**.
- Common symptoms include gastrointestinal (belching, pain, vomiting, nausea), skin (burning, itching, tingling) and sexual and menstrual complaints. They are **not usually bizarre**.
- Somatisation means the expression of psychological distress into bodily complaints for which medical help is sought.
- Patient **refuses** to accept advice or reassurance or negative test results.
- **Her** progress will be slower if she thinks her doctors do not believe her.
- Relatives should be involved, and
- **Empathy**, not persuasion, is the key to management ± antidepressives

### Hypochondrial disorder:

- Persistent belief in the presence of an underlying serious **DISEASE**, e.g. **C**ancer.
- Patient again refuses to accept reassurance or negative test results.

### Conversion disorder:

- Typically involves **loss of motor or sensory function**.
- **Some** patients may experience secondary **gain** from loss of function.

- **Psychogenic Aphonia** is a form of conversion disorder: not speaking after a shocking event.
- The patient doesn't consciously feign the symptoms (factitious disorder) or seek material gain (malingering).
- Patients may be indifferent to their apparent disorder - la belle indifference - although this has not been backed up by some studies.

**EX:** An 18-year-old sprinter who is currently preparing for a national athletics meeting. He describes a numb sensation below his knee. On examination the patient there is apparent sensory loss below the right knee in a non-dermatomal distribution. The team doctor suspects a non-organic cause of his symptoms. This is an example of a Conversion disorder.

**EX:** A 16-year-old girl is brought for review by her father. She is talented violinist and is due to start Music College in a few weeks' time. Her parents are concerned she has had a stroke as she is reporting weakness on her right side. Neurological examination is inconsistent and you suspect a non-organic cause for her symptoms. Despite reassurance about the normal examination findings the girl remains unable to move her right arm. What is the most appropriate term for this behaviour? >> This is a typical conversion disorder. There may be underlying tension regarding her musical career which be manifesting itself as apparent limb weakness.

## Dissociative disorder:

- Dissociation is a process of 'separating off' certain memories from normal consciousness.
- In contrast to conversion disorder **involves psychiatric symptoms e.g. Amnesia, fugue, stupor.**
- Dissociative identity disorder (DID) is the new term for multiple personality disorder as is the most severe form of dissociative disorder.

## Munchausen's syndrome:

- Also known as **factitious disorder.**
- The intentional production of physical or psychological symptoms.

## Malingering:

- Fraudulent simulation or exaggeration of symptoms with the intention of financial or other **gain.**

**EX:** A 24-year-old male is admitted to the ED complaining of severe abdominal pain. On examination he is shivering and rolling around the trolley. He has previously been investigated for abdominal pain and no cause has been found. He states that unless he is given morphine for the pain he will kill himself. >> He is malingering as the patient is reporting symptoms with the deliberate intention of getting morphine.

**EX:** A 46-year-old man is seen by an occupation health doctor due to long-term sickness leave. He states chronic lower back pain prevents him from working but examination findings are inconsistent and the doctor suspects a non-organic cause of his symptoms. >>> This is an example of a malingering.

## Anorexia nervosa

Anorexia nervosa is associated with a number of characteristic clinical signs and physiological abnormalities which are summarised below

### Features

- reduced body mass index
- bradycardia
- hypotension
- enlarged salivary glands

### Physiological abnormalities

- hypokalaemia
- low FSH, LH, oestrogens and testosterone
- raised cortisol and growth hormone
- impaired glucose tolerance
- hypercholesterolaemia
- hypercarotinaemia
- low T3

**Anorexia features:**

- **Most** things **low,** Except:
  **3G**'s and **3C's raised**: **g**rowth hormone, **g**lucose, salivary **g**lands, **c**ortisol, **c**holesterol, **c**arotinaemia.

Hospitalized patients with anorexia nervosa and **NGT** feeding are at risk of **refeeding syndrome**, which can lead to **profound hypophosphatemia**.

**Refeeding syndrome** is defined as the clinical complications which arise as a consequence of fluid and electrolyte shifts during the nutritional support of malnourished patients.

Refeeding syndrome comprises: **Hypo**phosphatemia, **Hypo**kalaemia, **Hypo**magnesaemia, Deficiencies in vitamins, for example, thiamine and trace minerals, and Fluid overload with oedema.

EX: Female pt. 15 years old has **primary amenorrhoea**, **loss of weight**, low BMI, **occasional diarrhoea**, **anaemia Hb is 10 gm%**, low FSH, low LH, and low Oestradiol but with normal testosterone, normal TSH, **low albumin** >>> **Coeliac disease not** anorexia nervosa.

## Bulimia nervosa

Bulimia nervosa is a type of eating disorder characterised by episodes of binge eating followed by intentional vomiting or other purgative behaviours such as the use of laxatives or diuretics or exercising.

### DSM 5 diagnostic criteria for a diagnosis of bulimia nervosa:

- recurrent episodes of **binge eating** (eating an amount of food that is definitely larger than most people would eat during a similar period of time and circumstances)
- a sense of lack of control over eating during the episode
- recurrent inappropriate compensatory behaviour in order to prevent weight gain, such as self-induced vomiting, misuse of laxatives, diuretics, or other medications, fasting, or excessive exercise.
  - recurrent vomiting may lead to **erosion of teeth** and Russell's sign - calluses on the knuckles or back of the hand due to repeated self-induced vomiting
- the binge eating and compensatory behaviours both occur, on average, at least once a week for three months.
- self-evaluation is unduly influenced by body shape and weight.
- the disturbance does not occur exclusively during episodes of anorexia nervosa.

## Management

- referral for specialist care is appropriate in all cases
- NICE recommend bulimia-nervosa-focused guided self-help for adults
- If bulimia-nervosa-focused guided self-help is unacceptable, contraindicated, or ineffective after 4 weeks of treatment, NICE recommend that we consider individual eating-disorder-focused cognitive behavioural therapy (CBT-ED)
- children should be offered bulimia-nervosa-focused family therapy (FT-BN)
- pharmacological treatments have a limited role - a trial of high-dose fluoxetine is currently licensed for bulimia but long-term data is lacking

- **EX**: Young female patient has **tooth erosion** associated with **hyponatremia**, **hypokalaemic metabolic alkalosis, low urea** & **hypocalcaemia** with ↑ **ALP**.

- If **severe hypokalaemia** with **low urinary K less than 1 mmol/l** (Normal: 25-100 mmol/l) >>> this fit with **laxative abuse** leading to increase GIT K loss and renal conservation of K >>> **Urinary screen for laxatives**.

## Hypomania vs. mania

| Mania | Hypomania |
|---|---|
| • Lasts for at least 7 days - Causes severe functional impairment in social and work setting<br>• May require hospitalization due to risk of harm to self or others<br>• May present with **psychotic symptoms** | • A lesser version of mania<br>• Lasts for < 7 days, typically 3-4 days. Can be high functioning and does not impair functional capacity in social or work setting<br>• Unlikely to require hospitalization<br>• Does not exhibit any psychotic symptoms |

**Therefore, the length of symptoms, severity and presence of psychotic symptoms (e.g. delusions of grandeur, auditory hallucinations) helps differentiates mania from hypomania.**

## The following symptoms are common to both hypomania and mania

### Mood

- predominately elevated
- irritable

### Speech and thought

- pressured
- flight of ideas: characterised by rapid speech with frequent changes in topic based on associations, distractions or word play
- poor attention

### Behaviour

- insomnia
- loss of inhibitions: sexual promiscuity, overspending, risk-taking
- increased appetite

# Post-traumatic stress disorder (PTSD)

PTSD can develop in people of any age following a traumatic event, for example a major disaster or childhood sexual abuse or sudden death of his small children.

It encompasses what became known as **'shell shock'** following the First World War.

One of the DSM-IV diagnostic criteria is that symptoms have been present for more than one month.

In PTSD the **onset** of symptoms is usually **delayed** and it tends to run a **prolonged course.**

## Features:

- **Re-experiencing**: **flashbacks**, **nightmares**, repetitive and distressing intrusive images.
- **Avoidance**: avoiding people, situations or circumstances resembling or associated with the event.
- **Hyperarousal**: hypervigilance for threat, exaggerated startle response, sleep problems, **insomnia**, **irritability** and **difficulty concentrating**.
- **Emotional numbing** - lack of ability to experience feelings, feeling detached.

- **Depression**.
- Drug or alcohol misuse.
- Anger.
- Unexplained physical symptoms

### Management:

- Following a traumatic event single-session interventions (often referred to as debriefing) are not recommended.
- Watchful waiting may be used for mild symptoms lasting less than 4 weeks.
- Military personnel have access to treatment provided by the armed forces.
- **trauma-focused cognitive behavioural therapy (CBT)** or eye movement desensitization and reprocessing (EMDR) therapy may be used in more severe cases
- drug treatments for PTSD should not be used as a routine first-line treatment for adults. If drug treatment is used then **venlafaxine or a selective serotonin reuptake inhibitor (SSRI)**, such as sertraline should be tried. In severe cases, NICE recommends that risperidone may be used.

## Post-concussion syndrome

Post-concussion syndrome is seen after even minor head trauma

### Typical features include

- headache
- fatigue
- anxiety/depression
- dizziness

## Grief reaction

It is normal for people to feel sadness and grief following the death of a loved one and this does not necessarily need to be medicalised.
However, having some understanding of the potential stages a person may go through whilst grieving can help determine whether a patient is having a 'normal' grief reaction or is developing a more significant problem.

**One of the most popular models of grief divides it into 5 stages.**

- Denial: this may include a feeling of numbness and also pseudo-hallucinations of the deceased, both auditory and visual. Occasionally people may focus on physical objects that remind them of their loved one or even prepare meals for them
- Anger: this is commonly directed against other family members and medical professionals
- Bargaining
- Depression
- Acceptance

**It should be noted that many patients will not go through all 5 stages.**

- Abnormal, or atypical, grief reactions are more likely to occur in women and if the death is sudden and unexpected.
- Other risk factors include a problematic relationship before death or if the patient has not much social support.

### Features of atypical grief reactions include:

- delayed grief: sometimes said to occur when more than 2 weeks passes before grieving begins
- prolonged grief: difficult to define. Normal grief reactions may take up to and beyond 12 months

## Depression

### Screening

The following two questions can be used to screen for depression

- 'During the last month, have you often been bothered by feeling down, depressed or hopeless?'
- 'During the last month, have you often been bothered by having little interest or pleasure in doing things?'

A 'yes' answer to either of the above should prompt a more in depth assessment.

### Assessment

There are many tools to assess the degree of depression including the Hospital Anxiety and Depression (HAD) scale and the Patient Health Questionnaire (PHQ-9).

### Hospital Anxiety and Depression (HAD) scale

- consists of 14 questions, 7 for anxiety and 7 for depression
- each item is scored from 0-3
- produces a score out of 21 for both anxiety and depression
- severity: 0-7 normal, 8-10 borderline, 11+ case
- patients should be encouraged to answer the questions quickly

### Patient Health Questionnaire (PHQ-9)

- asks patients 'over the last 2 weeks, how often have you been bothered by any of the following problems?'
- 9 items which can then be scored 0-3
- includes items asking about thoughts of self-harm
- depression severity: 0-4 none, 5-9 mild, 10-14 moderate, 15-19 moderately severe, 20-27 severe

### NICE use the DSM-IV criteria to grade depression:

- Depressed mood most of the day, nearly every day
- Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day
- Significant weight loss or weight gain when not dieting or decrease or increase in appetite nearly every day
- Insomnia or hypersomnia nearly every day
- Psychomotor agitation or retardation nearly every day
- Fatigue or loss of energy nearly every day
- Feelings of worthlessness or excessive or inappropriate guilt nearly every day
- Diminished ability to think or concentrate, or indecisiveness nearly every day
- Recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide

| Subthreshold depressive symptoms | Fewer than 5 symptoms |
|---|---|
| **Mild depression** | Few, if any, symptoms in excess of the 5 required to make the diagnosis, and symptoms result in only minor functional impairment |
| **Moderate depression** | Symptoms or functional impairment are between 'mild' and 'severe' |
| **Severe depression** | Most symptoms, and the symptoms markedly interfere with functioning. Can occur with or without psychotic symptoms |

## Depression in older people

Older patients are less likely to complain of depressed mood

### Features

- physical complaints (e.g. hypochondriasis)
- agitation
- insomnia

### Management

- SSRIs are first line (adverse side-effect profile of TCAs more of an issue in the elderly)

## Depression vs. dementia

Factors suggesting diagnosis of depression over dementia

- short history, rapid onset
- biological symptoms e.g. weight loss, sleep disturbance
- patient worried about poor memory
- reluctant to take tests, disappointed with results
- mini-mental test score: variable
- **global memory loss (dementia characteristically causes recent memory loss)**

# Suicide

**The risk stratification of psychiatric patients into 'high', 'medium' or 'low risk' is common in clinical practice.** Questions based on a patient's suicide risk are therefore often seen. However, it should be noted that there is a paucity of evidence addressing the positive predictive value of individual risk factors.

An interesting review in the BMJ (BMJ 2017;359:j4627) concluded that 'there is no evidence that these assessments can usefully guide decision making' and noted that 50% of suicides occur in patients deemed 'low risk'.

Whilst the evidence base is relatively weak, there are a number of factors shown to be associated with an increased risk of suicide

- male sex (hazard ratio (HR) approximately 2.0)
- history of deliberate self-harm (HR 1.7)
- alcohol or drug misuse (HR 1.6)
- history of mental illness
  - depression
  - schizophrenia: NICE estimates that 10% of people with schizophrenia will complete suicide

- history of chronic disease
- advancing age
- unemployment or social isolation/living alone
- being unmarried, divorced or widowed

If a patient has actually attempted suicide, there are a number of factors associated with an increased risk of completed suicide at a future date:

- efforts to avoid discovery
- planning
- leaving a written note
- final acts such as sorting out finances
- violent method

## Protective factors

There are, of course, factors which reduce the risk of a patient committing suicide. These include

- family support
- having children at home
- religious belief

- In an Emergency Department the suicidal patient who declines to be admitted for observation arid treatment should be managed as follows:
  - Ensure that a member of staff stays with them at all times
  - Call the duty psychiatrist
  - **If they attempt to abscond before or during psychiatric assessment, the staff of the Emergency Department have a duty under Common Law to restrain the patient**

**A suicidal patient became agitated and insisted that she wanted to go home immediately. How should you proceed?**

**Call the duty psychiatrist, and with other staff in the Emergency Department attempt to restrain her until they arrive**

# Generalized anxiety disorder and panic disorder

**Anxiety is a common disorder that can present in multiple ways. NICE define the central feature as an 'excessive worry about a number of different events associated with heightened tension.'**

Always look for a potential physical cause when considering a psychiatric diagnosis.
In anxiety disorders, important alternative causes include hyperthyroidism, cardiac disease and medication-induced anxiety (NICE).
Medications that may trigger anxiety include salbutamol, theophylline, corticosteroids, antidepressants and caffeine

## Management of generalised anxiety disorder (GAD)

### NICE suggest a step-wise approach:

- step 1: education about GAD + active monitoring
- step 2: low-intensity psychological interventions (individual non-facilitated self-help or individual guided self-help or psychoeducational groups)
- step 3: high-intensity psychological interventions (cognitive behavioural therapy or applied relaxation) or drug treatment. See drug treatment below for more information
- step 4: highly specialist input e.g. Multi agency teams

### Drug treatment

- NICE suggest sertraline should be considered the first-line SSRI
- If sertraline is ineffective, offer an alternative SSRI or a serotonin–noradrenaline reuptake inhibitor (SNRI)
  - examples of SNRIs include duloxetine and venlafaxine
- If the person cannot tolerate SSRIs or SNRIs, consider offering pregabalin
- interestingly for patients under the age of 30 years NICE recommend you warn patients of the increased risk of suicidal thinking and self-harm. Weekly follow-up is recommended for the first month

## Management of panic disorder

### Again a stepwise approach:

- step 1: recognition and diagnosis
- step 2: treatment in primary care - see below
- step 3: review and consideration of alternative treatments
- step 4: review and referral to specialist mental health services
- step 5: care in specialist mental health services

### Treatment in primary care

- NICE recommend either cognitive behavioural therapy or drug treatment
- SSRIs are first-line. If contraindicated or no response after 12 weeks then imipramine or clomipramine should be offered

- **EX:** A 35-year-old woman presents with shortness of breath, palpitations and anxiety.
- The episodes have been occurring over 3 years, but are worse recently. The episodes occur at stressful periods and are also related to difficult tasks at work. There is no history of drug or alcohol abuse.
- The most appropriate pharmacological management for this patient >> **SSRI (Paroxetine) (Seroxat 20 mg tablet).**

## Mood disorder

### Cyclothymic disorder

numerous periods of both depression (but not major depressive episodes) and hypomania for at least two years.

- The crucial feature of a major depressive disorder is a severe dysphoric mood and persistent loss of interest or pleasure in all usual activities.

### Dysthymic disorder

chronic depression with never a manic or hypomanic episode, for at least two years.

### Bipolar I disorder

severe alterations in mood (**mania and depression**) that are usually episodic and recurrent.

**Treatment**

- Sodium valproate and carbamazepine are efficacious as first line treatment in the prophylaxis of manic and depressive episodes in bipolar I disorder. Lithium may be used if these anticonvulsants are ineffective.
- However, in the initial stages of manic episodes, the addition of drugs with potent sedative effects are often required, for example, clonazepam, lorazepam and haloperidol.
  - These drugs can be tapered and then discontinued as soon as the initial phase of the manic episode has subsided, and the effects of the anticonvulsants or lithium are seen clinically.

**Bipolar II disorder:** characterised by one or more major **depressive** episodes, at least one **hypomanic** episode and **NO manic** episodes.

## Cognitive behavioural therapy (CBT)

### Main points:

- Useful in the management of **depression** and **anxiety** disorders.
- Can be used for patients already taking antidepressants.
- Usually consists of **one to two hour sessions once per week.**
- **Should be completed within 6 months.**
- Patients usually get around **16-20 hours in total.**

## Seasonal affective disorder

Seasonal affective disorder (SAD) describes **depression which occurs predominately around the winter months.**
SAD should be treated the same way as depression, therefore as per the NICE guidelines for mild depression, you would begin with psychological therapies and follow up with the patient in 2 weeks to ensure that there has been no deterioration.
Following this an SSRI can be given if needed. In seasonal affective disorder, you should not give the patient sleeping tablets as this can make the symptoms worse.
Finally, the evidence for light therapy is limited and as such it is not routinely recommended.

## Body dysmorphic disorder

Body dysmorphic disorder (sometimes referred to as dysmorphophobia) is a mental disorder where patients have a significantly distorted body image

### Diagnostic and Statistical Manual (DSM) IV criteria:

- Preoccupation with an imagine defect in appearance. If a slight physical anomaly is present, the person's concern is markedly excessive
- The preoccupation causes clinically significant distress or impairment in social, occupational, or other important areas of functioning
- The preoccupation is not better accounted for by another mental disorder (e.g., dissatisfaction with body shape and size in Anorexia Nervosa)

# Post-partum mental health problems

Post-partum mental health problems range from the 'baby-blues' to puerperal psychosis.

The **Edinburgh Postnatal Depression Scale** may be used to screen for depression:

- 10-item questionnaire, with a maximum score of 30
- indicates how the mother has felt over the previous week
- score > 13 indicates a 'depressive illness of varying severity'
- sensitivity and specificity > 90%
- includes a question about self-harm

| 'Baby-blues' | Postnatal depression | Puerperal psychosis |
|---|---|---|
| Seen in around 60-70% of women<br><br>Typically seen 3-7 days following birth and is more common in primips<br><br>Mothers are characteristically anxious, tearful and irritable | Affects around 10% of women<br><br>Most cases start within a month and typically peaks at 3 months<br><br>Features are similar to depression seen in other circumstances | Affects approximately 0.2% of women<br><br>Onset usually within the first 2-3 weeks following birth<br><br>Features include severe swings in mood (similar to bipolar disorder) and disordered perception (e.g. auditory hallucinations) |
| Reassurance and support, the health visitor has a key role | As with the baby blues reassurance and support are important<br><br>NICE CKS state *'Most women with the baby blues will not require specific treatment other than reassurance'*<br><br>Cognitive behavioural therapy may be beneficial. Certain SSRIs such as sertraline and paroxetine* may be used if symptoms are severe** - whilst they are secreted in breast milk it is not thought to be harmful to the infant | Admission to hospital is usually required, ideally in a Mother & Baby Unit<br><br>There is around a 25-50% risk of recurrence following future pregnancies |

*paroxetine is recommended by SIGN because of the low milk/plasma ratio

**fluoxetine is best avoided due to a long half-life

# Alcohol withdrawal

## Mechanism

- chronic alcohol consumption enhances GABA mediated inhibition in the CNS (similar to benzodiazepines) and **inhibits NMDA-type glutamate receptors**
- alcohol withdrawal is thought to be lead to the opposite (decreased inhibitory GABA and increased NMDA glutamate transmission)

## Features

- symptoms start at 6-12 hours: tremor, sweating, tachycardia, anxiety
- **peak incidence of seizures at 36 hours**
- peak incidence of delirium tremens is at 48-72 hours: coarse tremor, confusion, delusions, auditory and visual hallucinations, fever, tachycardia

## Management

- **patients with a history of complex withdrawals from alcohol (i.e. delirium tremens, seizures, blackouts) should be admitted to hospital for monitoring until withdrawals stabilised**
- first-line: long-acting benzodiazepines e.g. **chlordiazepoxide or diazepam. Lorazepam** may be preferable in patients with hepatic failure. Typically given as part of a reducing dose protocol
- carbamazepine also effective in treatment of alcohol withdrawal
- phenytoin is said not to be as effective in the treatment of alcohol withdrawal seizures

# Electroconvulsive therapy

Electroconvulsive therapy is a useful treatment option for patients with severe depression refractory to medication (e.g. catatonia) those with psychotic symptoms.
The only absolute contraindications is **raised intracranial pressure**.

## Short-term side-effects

- headache
- nausea
- short term memory impairment
- memory loss of events prior to ECT
- cardiac arrhythmia

## Long-term side-effects

- some patients report impaired memory

- Although ECT, by definition, causes a controlled seizure there is **NO increased risk of epilepsy in the long-term.**
- The **only absolute contraindications** is **raised intracranial pressure**.

- Although ECT has been safely used one month following a stroke, it is advisable to avoid treatment in the first three months.
- Most guidelines state that a **recent CVA (within 1 to 3 months)** is a **contraindication**.
- **ECT** would usually be **avoided** in a **recent cerebrovascular accident.**

# Charles-Bonnet syndrome

**Charles-Bonnet syndrome (CBS)** is characterized by persistent or recurrent **complex hallucinations (usually visual or auditory), occurring in clear consciousness.**
**This is generally against a background of visual impairment (although visual impairment is not mandatory for a diagnosis).**
**Insight is usually preserved.**
**This must occur in the absence of any other significant neuropsychiatric disturbance.**

## Risk factors include:

- Advanced age
- Peripheral visual impairment
- Social isolation
- Sensory deprivation
- Early cognitive impairment

**CBS is equally distributed between sexes and does not show any familial predisposition. The most common ophthalmological conditions associated with this syndrome are age-related macular degeneration, followed by glaucoma and cataract.**
Well-formed complex visual hallucinations are thought to occur in 10-30 per cent of individuals with severe visual impairment.
Prevalence of CBS in visually impaired people is thought to be between 11 and 15 per cent.
Around a third find the hallucinations themselves an unpleasant or disturbing experience.
In a large study published in the British Journal of Ophthalmology, 88% had CBS for 2 years or more, resolving in only 25% at 9 years (thus it is not generally a transient experience).

## Delusional parasitosis

Delusional parasitosis is a relatively rare condition where a patient has **a fixed, false belief (delusion) that they are infested by 'bugs'** e.g., worms, parasites, mites, bacteria, fungus.
This may occur in conjunction with other psychiatric conditions or may present by itself, with patients often otherwise quite functional despite the delusion.

## Delusions

### Cotard syndrome

Cotard syndrome is a rare mental disorder where the affected **patient believes that they (or in some cases just a part of their body) is either dead or non-existent.**
This delusion is often difficult to treat and can result in significant problems due to patients stopping eating or drinking as they deem it not necessary.

### Othello syndrome

is a delusional belief that a patients partner is committing infidelity despite no evidence of this. It can often result in violence and controlling behaviour.

### De Clerambault syndrome

(otherwise known as erotomania), is where a **patient believes that a person of a higher social or professional standing is in love with them.**
Often this presents with people who believe celebrities are in love with them.

### Ekbom syndrome

is also known as delusional parasitosis and is the **belief that they are infected with parasites or have 'bugs' under their skin.**
This can vary from the classic psychosis symptoms in narcotic use where the user can 'see' bugs crawling under their skin or can be a patient who believes that they are infested with snakes.

### Capgras delusion

is the belief that friends or family members have been replaced by an identical looking imposter.

## Personality disorders

**Personality disorders may be defined as a series of maladaptive personality traits that interfere with normal function in life.**
It is thought that around 1 in 20 people have a personality disorder.

They are typically categorised as belonging to one of three clusters:

| Cluster A: 'Odd or Eccentric' | Cluster B: 'Dramatic, Emotional, or Erratic' | Cluster C: 'Anxious and Fearful' |
|---|---|---|
| • Paranoid<br>• Schizoid<br>• Schizotypal | • Antisocial<br>• Borderline (Emotionally Unstable)<br>• Histrionic<br>• Narcissistic | • Obsessive-Compulsive<br>• Avoidant<br>• Dependent |

## Cluster A: 'Odd or Eccentric'

### Paranoid

- Hypersensitivity and an unforgiving attitude when insulted
- Unwarranted tendency to questions the loyalty of friends
- Reluctance to confide in others
- Preoccupation with conspirational beliefs and hidden meaning
- Unwarranted tendency to perceive attacks on their character

### Schizoid

- Indifference to praise and criticism
- Preference for solitary activities
- Lack of interest in sexual interactions
- Lack of desire for companionship
- Emotional coldness
- Few interests
- Few friends or confidants other than family

### Schizotypal

- Ideas of reference (differ from delusions in that some insight is retained)
- Odd beliefs and magical thinking
- Unusual perceptual disturbances
- Paranoid ideation and suspiciousness
- Odd, eccentric behaviour
- **Lack of close friends** other than family members
- Inappropriate affect
- Odd speech without being incoherent

## Cluster B: 'Dramatic, Emotional, or Erratic'

### Antisocial

- **Failure to conform to social norms** with respect to lawful behaviours as indicated by repeatedly performing acts that are grounds for arrest;
- More common in men;

- Deception, as indicated by repeatedly lying, use of aliases, or conning others for personal profit or pleasure;
- Impulsiveness or failure to plan ahead;
- Irritability and aggressiveness, as indicated by repeated physical fights or assaults;
- Reckless disregard for the safety of self or others;
- Consistent irresponsibility, as indicated by repeated failure to sustain consistent work behaviour or honour financial obligations;
- **Lack of remorse, as indicated by being indifferent to or rationalizing having hurt, mistreated, or stolen from another**

**Borderline - also known as Emotionally Unstable**

- **Efforts to avoid real or imagined abandonment**
- Unstable interpersonal relationships which alternate between idealization and devaluation
- Unstable self image
- Impulsivity in potentially self damaging area (e.g. Spending, sex, substance abuse)
- Recurrent suicidal behaviour
- Affective instability
- Chronic feelings of emptiness
- Difficulty controlling temper
- Quasi psychotic thoughts

**Histrionic**

- **Inappropriate sexual seductiveness**
- Need to be the center of attention
- Rapidly shifting and shallow expression of emotions
- Suggestibility
- Physical appearance used for attention seeking purposes
- Impressionistic speech lacking detail
- Self-dramatization
- Relationships considered to be more intimate than they are

**Narcissistic**

- Grandiose sense of self importance
- Preoccupation with fantasies of unlimited success, power, or beauty
- Sense of entitlement
- Taking advantage of others to achieve own needs
- Lack of empathy
- Excessive need for admiration
- Chronic envy
- Arrogant and haughty attitude

## Cluster C: 'Anxious and Fearful'

### Obsessive-compulsive

- Is occupied with details, rules, lists, order, organization, or agenda to the point that the key part of the activity is gone
- Demonstrates perfectionism that hampers with completing tasks
- Is extremely dedicated to work and efficiency to the elimination of spare time activities
- Is meticulous, scrupulous, and rigid about etiquettes of morality, ethics, or values
- Is not capable of disposing worn out or insignificant things even when they have no sentimental meaning
- Is unwilling to pass on tasks or work with others except if they surrender to exactly their way of doing things
- Takes on a stingy spending style towards self and others; and shows stiffness and stubbornness

### Avoidant

- Avoidance of occupational activities which involve significant interpersonal contact due to fears of criticism, or rejection.
- Unwillingness to be involved unless certain of being liked
- **Preoccupied with ideas that they are being criticised or rejected in social situations**
- Restraint in intimate relationships due to the fear of being ridiculed
- Reluctance to take personal risks due to fears of embarrassment
- Views self as inept and inferior to others
- Social isolation accompanied by a craving for social contact

### Dependent

- **Difficulty making everyday decisions without excessive reassurance from others**
- Need for others to assume responsibility for major areas of their life
- Difficulty in expressing disagreement with others due to fears of losing support
- Lack of initiative
- Unrealistic fears of being left to care for themselves
- Urgent search for another relationship as a source of care and support when a close relationship ends
- Extensive efforts to obtain support from others
- Unrealistic feelings that they cannot care for themselves

### Management

Personality disorders are difficult to treat and, in the past, have been considered 'untreatable' by definition. However, a number of approaches have been shown to help patients, including:

- psychological therapies: dialectical behavior therapy
- treatment of any coexisting psychiatric conditions.

## Chronic fatigue syndrome (CFS)

It is diagnosed after at least 4 months of disabling fatigue affecting mental and physical function more than 50% of the time in the absence of other disease which may explain symptoms.

### Epidemiology:

- More common in **females**.
- Past psychiatric history has not been shown to be a risk factor.

In general, in order to receive a **diagnosis** of chronic fatigue syndrome, a patient must satisfy **two criteria**.

**First**, they must have **severe chronic fatigue of 6 months or longer duration** with other known **medical** conditions **excluded** by clinical diagnosis.

**Secondly**, they must concurrently have 4 or more of the following symptoms:

**Fatigue is the central feature, other recognised features include:**

- Sleep disorders.
- Muscle and/or Multi-joint pain without swelling or redness.
- Headache of a new type
- Painful LN without enlargement.
- Sore throat.
- Cognitive dysfunction: difficulty thinking, inability to concentrate, impairments of short-term memory.
- General malaise or flu like symptoms.
- Dizziness
- Nausea
- Palpitations

### Investigations:

NICE guidelines suggest carrying out a large number of screening blood tests to exclude other pathology e.g.: CBC, ESR, CRP, U&E, LFT, RBS, TFT, Calcium, Ferritin, coeliac disease screening and urine analysis.

### Management:

- **CBT**: very effective, number needed to treat = 2
- Graded exercise therapy: a formal supervised program, don't advice to go to the gym.
- Low dose amitriptyline may be useful for poor sleep.
- Referral to pain management clinic if pain is a predominant feature.

Good prognosis in children

## Restless leg syndrome (RLS)

It is a **spontaneous continuous** lower limb movement that may be associated with **paraesthesia**.

It is extremely common, affecting between **2 – 10%** of the general population. Males and females are **equally** affected and a family history may be present.

### Clinical features:

- Uncontrollable urge to move legs (akathisia). Symptoms initially occur at night but as condition progresses may occur during the day.
- Symptoms worse at rest.
- **Paraesthesia** e.g. crawling or throbbing sensations.
- Movement during sleep may be noted by the partner: periodic limb movements of sleeps (PLMS).

### Causes and associations:

- There is **+ve family history** in **50%** of patients with **idiopathic** RLS.
- **Iron deficiency anaemia (IDA)**.
- **Uraemia**.
- **DM**
- **Pregnancy**

**The diagnosis** is clinical although CBC to exclude IDA may be appropriate.

### Management:

- Simple measures: walking, stretching, massaging of affected limb.
- Treat **IDA**
- **Dopamine agonists** are first line **Pramipexole (Sifrol®)**, **Ropinirole (Requip®)**.
- Benztropine: (cogintol)
- Gabapentin

# Geriatric medicine

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# Dementia

Dementia is thought to affect over 700,000 people in the UK and accounts for a large amount of health and social care spending.

The most common cause of dementia in the UK is Alzheimer's disease followed by vascular and Lewy body dementia. These conditions may coexist.

## Features

- diagnosis can be difficult and is often delayed
- assessment tools recommended by NICE for the non-specialist setting include: 10-point cognitive screener (10-CS), 6-Item cognitive impairment test (6CIT)
- assessment tools **not** recommended by NICE for **the non-specialist** setting include the abbreviated mental test score (AMTS), General practitioner assessment of cognition (GPCOG) and the mini-mental state examination (MMSE) have been widely used. **A MMSE score of 24 or less out of 30 suggests dementia**

## Management

- in primary care, a blood screen is usually sent to exclude reversible causes (e.g. Hypothyroidism). NICE recommend the following tests: FBC, U&E, LFTs, calcium, glucose, ESR/CRP, TFTs, vitamin B12 and folate levels. Patients are now commonly referred on to old-age psychiatrists (sometimes working in 'memory clinics').
- in secondary care, **neuroimaging** is performed* to exclude other reversible conditions (e.g. Subdural haematoma, normal pressure hydrocephalus) and help provide information on aetiology to guide prognosis and management

***in the NICE guidelines structural imaging was said to be essential in the investigation of dementia**

# Dementia causes

| 1ry dementia (85%) | 2ry dementia (15%) |
|---|---|
| **Alzheimer Dementia.**<br>**Fronto-temporal Dementia.**<br>**Creutzfeldt - Jackob Disease.**<br>**Parkinson plus :**<br>• cortico-basilar degeneration.<br>• Progressive Supranuclear Palsy.<br>• Parkinson Disease with dementia.<br>**Others:**<br>• Vascular dementia<br>• Normal pressure Hydrocephalus | **Can be (reversible)**<br>**Metabolic**<br>• vit B12, folate, thiamine hypothyroidism<br>• Cushing's S<br>• Wilson's D.<br>**Vascular**<br>• CVA.<br>• Subdural Hematoma.<br>• 1ry angiitis of CNS.<br>• Antiphospholipid syndrome.<br>**Neoplastic**<br>**CNS tumours.**<br>**mets.**<br>**Drugs & toxins**<br>• anti cholinergic.<br>• Ch. Alcoholism.<br>• Heavy metals.<br>**Infections**<br>• Syphilis.<br>• AIDs - dementia complex. |

**Important differentials, potentially treatable**

- hypothyroidism, Addison's
- B12/folate/thiamine deficiency
- syphilis
- brain tumour
- normal pressure hydrocephalus
- subdural haematoma
- depression
- chronic drug use e.g., Alcohol, barbiturates.

# Confusion

## Is either delirium or dementia

**1. Acute confusional state**
Acute confusional state is also known as **delirium or acute organic brain syndrome**. It affects up to 30% of elderly patients admitted to hospital.it consists of fluctuation in consciousness and cognitive functions.

**2. Dementia: chronic impairment of cognitive functions.**

# Alzheimer's disease

## Pathophysiology

Alzheimer's disease (AD) is a progressive degenerative disease of the brain accounting for the majority of dementia seen in the UK.

## Risk factors

- increasing age
- family history of Alzheimer's disease
- 5% of cases are inherited as an autosomal dominant trait
  - mutations in the amyloid precursor protein (chromosome 21), presenilin 1 (chromosome 14) and presenilin 2 (chromosome 1) genes are thought to cause the inherited form
- apoprotein E allele E4 - encodes a cholesterol transport protein
- Caucasian ethnicity
- Down's syndrome

## Pathological changes

- macroscopic:
  - widespread cerebral atrophy, particularly involving the cortex and hippocampus
- microscopic:
  - cortical plaques due to deposition of type A-Beta-amyloid protein and intraneuronal neurofibrillary tangles caused by abnormal aggregation of the tau protein
  - hyperphosphorylation of the tau protein has been linked to AD
- biochemical
  - there is a deficit of acetylcholine from damage to an ascending forebrain projection

## Neurofibrillary tangles

- paired helical filaments are partly made from a protein called tau
- tau is a protein that interacts with tubulin to stabilize microtubules and promote tubulin assembly into microtubules
- in AD are tau proteins are excessively phosphorylated, impairing its function.

### Management

Alzheimer's disease is a progressive degenerative disease of the brain accounting for the majority of dementia seen in the UK

**Non-pharmacological management**

- NICE recommend *offering* 'a range of activities to promote wellbeing that are tailored to the person's preference'
- NICE recommend *offering* group cognitive stimulation therapy for patients with mild and moderate dementia
- other options to *consider* include group reminiscence therapy and cognitive rehabilitation

**Pharmacological management**

- NICE updated its dementia guidelines in 2018
- the three acetylcholinesterase inhibitors **(donepezil, galantamine and rivastigmine)** as options for managing mild to moderate Alzheimer's disease
- **memantine** (an NMDA receptor antagonist) is in simple terms the **'second-line'** treatment for Alzheimer's, NICE recommend it is used in the following situation reserved for patients with
  - moderate Alzheimer's who are intolerant of, or have a contraindication to, acetylcholinesterase inhibitors
  - as an add-on drug to acetylcholinesterase inhibitors for patients with moderate or severe Alzheimer's
  - monotherapy in severe Alzheimer's

## Managing non-cognitive symptoms

- NICE does not recommend antidepressants for mild to moderate depression in patients with dementia
- **antipsychotics** should only be used for patients at risk of harming themselves or others, or when the agitation, hallucinations or delusions are causing them severe distress

**Donepezil**

- **is relatively contraindicated in patients with bradycardia**
- adverse effects include **insomnia**

# Vascular dementia

**Vascular dementia (VD) is the second most common form of dementia after Alzheimer disease.**

It is not a single disease but a group of syndromes of cognitive impairment caused by different mechanisms causing ischemia or hemorrhage secondary to cerebrovascular disease.

Vascular dementia has been increasingly recognized as the most severe form of the spectrum of deficits encompassed by the term vascular cognitive impairment (VCI).
Early detection and an accurate diagnosis are important in the prevention of vascular dementia.

## Epidemiology

- VD is thought to account for around 17% of dementia in the UK
- Prevalence of dementia following a first stroke varies depending on location and size of the infarct, definition of dementia, interval after stroke and age among other variables. Overall, stroke doubles the risk of developing dementia.
- Incidence increases with age

## The main subtypes of VD:

- Stroke-related VD – multi-infarct or single-infarct dementia
- Subcortical VD – caused by small vessel disease
- Mixed dementia – the presence of both VD and Alzheimer's disease

## Risk factors

- History of stroke or transient ischemic attack (TIA)
- Atrial fibrillation
- Hypertension
- Diabetes mellitus
- Hyperlipidemia
- Smoking
- Obesity
- Coronary heart disease
- A family history of stroke or cardiovascular

Rarely, VD can be inherited as in the case of CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy.

## Patients with VD typically presents with

- Several months or several years of a history of a sudden or **stepwise deterioration** of cognitive function.

## Symptoms and the speed of progression vary but may include:

- Focal neurological abnormalities e.g. visual disturbance, sensory or motor symptoms
- The difficulty with attention and concentration
- Seizures
- Memory disturbance
- Gait disturbance
- Speech disturbance
- Emotional disturbance

## Diagnosis is made based on:

- A comprehensive history and physical examination
- Formal screen for cognitive impairment
- Medical review to exclude medication cause of cognitive decline
- MRI scan – may show infarcts and extensive white matter changes

National Institute for health and care excellence (NICE) recommends that diagnosis be made using the NINDS-AIREN criteria for probable vascular dementia

| |
|---|
| Presence of cognitive decline that interferes with activities of daily living, not due to secondary effects of the cerebrovascular event<br>• established using clinical examination and neuropsychological testing |
| Cerebrovascular disease<br>• defined by neurological signs and/or brain imaging |
| A relationship between the above two disorders inferred by:<br>• the onset of dementia within three months following a recognised stroke<br>• an abrupt deterioration in cognitive functions<br>• fluctuating, stepwise progression of cognitive deficits |

## General management

- Treatment is mainly symptomatic with the aim to address individual problems and provide support to the patient and carers
- Important to detect and address cardiovascular risk factors – for slowing down the progression

## Non-pharmacological management

- Tailored to the individual
- Include: cognitive stimulation programmes, multisensory stimulation, music and art therapy, animal-assisted therapy
- Managing challenging behaviours e.g. address pain, avoid overcrowding, clear communication

### Pharmacological management

- There is no specific pharmacological treatment approved for cognitive symptoms
- Only consider **AChE inhibitors** or memantine for people with vascular dementia if they have suspected comorbid Alzheimer's disease, Parkinson's disease dementia or dementia with Lewy bodies.
- There is no evidence that aspirin is effective in treating patients with a diagnosis of vascular dementia.
- No randomized trials found evaluating statins for vascular dementia

## Frontotemporal lobar degeneration

Frontotemporal lobar degeneration (FTLD) is the third most common type of cortical dementia after Alzheimer's and Lewy body dementia.

### There are three recognized types of FTLD

- Frontotemporal dementia (Pick's disease)
- Progressive non fluent aphasia (chronic progressive aphasia, CPA)
- Semantic dementia

| Common features of frontotemporal lobar dementias |
|---|
| Onset before 65 |
| Insidious onset |
| Relatively preserved memory and visuospatial skills |
| Personality change and social conduct problems |

### Pick's disease

This is the most common type and is characterized by personality change and impaired social conduct. Other common features include hyperorality, disinhibition, increased appetite, and perseveration behaviors.

**Focal gyral atrophy with a knife-blade appearance is characteristic of Pick's disease.**

### Macroscopic changes seen in Pick's disease include:-

- Atrophy of the frontal and temporal lobe.

### Microscopic changes include:-

- Pick bodies - spherical aggregations of tau protein (silver-staining)
- Gliosis
- Neurofibrillary tangles
- Senile plaques

**Management:** NICE do not recommend that AChE inhibitors or memantine are used in people with frontotemporal dementia

### CPA

Here the chief factor is non- fluent speech. They make short utterances that are agrammatic.
Comprehension is relatively preserved.

### Semantic dementia

Here the patient has a fluent progressive aphasia.
The speech is fluent but empty and conveys little meaning. Unlike in Alzheimer's memory is better for recent rather than remote events.

## Lewy body dementia

Lewy body dementia is an increasingly recognized cause of dementia, accounting for up to 20% of cases.
The characteristic pathological feature is alpha-synuclein cytoplasmic inclusions (Lewy bodies) in the substantia nigra, paralimbic and neocortical areas.

The relationship between Parkinson's disease and Lewy body dementia is complicated, particularly as dementia is often seen in Parkinson's disease. Also, up to 40% of patients with Alzheimer's have Lewy bodies.

### Features

- progressive cognitive impairment
  - in contrast to Alzheimer's, early impairments in attention and executive function rather than just memory loss
  - cognition may be fluctuating, in contrast to other forms of dementia
  - usually develops before parkinsonism
- parkinsonism
- **visual hallucinations** (other features such as delusions and non-visual hallucinations may also be seen)

### Diagnosis

- usually clinical
- single-photon emission computed tomography (SPECT) is increasingly used.
- It is currently commercially known as a DaTscan. Dopaminergic iodine-123-radiolabelled 2-carbomethoxy-3-(4-iodophenyl)-N-(3-fluoropropyl) nortropane (123-I FP-CIT) is used as the radioisotope. The sensitivity of SPECT in diagnosing Lewy body dementia is around 90% with a specificity of 100%

## Management

- both acetylcholinesterase inhibitors (e.g. donepezil, rivastigmine) and memantine can be used as they are in Alzheimer's. NICE have made detailed recommendations about what drugs to use at what stages. Please see the link for more details
- neuroleptics should be avoided in Lewy body dementia as patients are extremely sensitive and may develop irreversible parkinsonism. Questions may give a history of a patient who has deteriorated following the introduction of an antipsychotic agent

# Delirium

**Predisposing factors include:**

- age > 65 years
- background of dementia
- significant injury e.g. hip fracture
- frailty or multimorbidity polypharmacy

**The precipitating events are often multifactorial and may include:**

- infection: particularly urinary tract infections
- metabolic: e.g. hypercalcaemia, hypoglycaemia, hyperglycaemia, dehydration
- **change of environment**
- any significant cardiovascular, respiratory, neurological or endocrine condition
- severe pain
- alcohol withdrawal
- **constipation**

## causes and classification according to age.

- Infection.
- Hepatic encephalopathy.
- Uremia.
- Drugs.
- Alcohol: Wernicke and delirium tremens.
- Polypharmacy.
- Subdural hematoma.
- Fecal impaction.
- Urinary retention.
- Electrolyte disturbance.
- M.I and PE.
- HIV.

| < 65 yrs | > 65 yrs | In all Ages |
|---|---|---|
| Recreation drugs Withdrawal.<br>Meningitis / encephalopathy.<br>HIV / AIDS. | *polypharmacy<br>*stroke/ subdural Hemorrhage.<br>*Infection.<br>*U.T. retention.<br>*Fecal impaction. | Electrolyte imbalance.<br>Infections.<br>Metabolic : liver, renal, thyroid<br>Cerebral Tumors or Mets.<br>Infarction:<br>P.E / M.I.<br>Alcohol: withdrawal or Werneck's encephalopathy. |

## Features - a wide variety of presentations

- memory disturbances (loss of short term > long term)
- may be very agitated or withdrawn
- disorientation
- mood change
- visual hallucinations
- disturbed sleep cycle
- poor attention

## Indication of C.T scan in patient with confusion:

- No cause of confusion from routine investigations
- History of head trauma.
- History of neurological cause: limb weakness, sudden onset, headache seizures, suspected metastasis.
- Exclude Mass lesion before lumbar puncture.
- HIV/AIDS patient with confusion.

## Parkinsonism with dementia:

management can be challenging in patients with Parkinson's disease, as antipsychotics can often worsen Parkinsonian symptoms careful reduction of the Parkinson medication may be helpful.

- Anticholinergics (benztropine, procyclidine).
- Dopamine agonists: Levodopa.
- Lewy body dementia.

## Parkinson's Disease with dementia differentials

| **Cognitive impairment before or within one year of with extrapyramidal symptoms** | **Cognitive impairment More than one year with Motor symptoms.** |
|---|---|
| = dementia with Lewy bodies:<br>1) difficult in counting things.<br>2) fluctuate.<br>3) visual hallucinations. | = parkinsonism disease dementia. |

## Summary of treatment

- Supportive treatment: in a quiet room.
- Medical treatment: treatment underlying cause
- Review patient medications & stop offending treatment .

**Sedations:**

| Benzodiazepines | Antipsychotics |
|---|---|
| • lorazepam in Alcohol withdrawal. (+/-Haloperidol ) | • Haloperidol<br>• Olanzapine / risperidone (Contraindicated In CVA) |

if symptoms require urgent treatment, then the atypical antipsychotics quetiapine and clozapine are preferred

# Delirium vs. dementia

## Factors favoring delirium over dementia

- **Impairment/fluctuation of consciousness**
- **fluctuation of symptoms:** worse at night, periods of normality
- abnormal perception (e.g., illusions and hallucinations)
- agitation, fear
- delusions

## Differentiate delirium from dementia

| Delirium | Dementia |
|---|---|
| **Reversable**<br>**Sudden onset / fluctuating impairment in cognitive function and consciousness** | **Progressive, irreversible decline in global cognitive function without change in conscious level** |

**Acute delirium on top of chronic confusion = impaired consciousness in patient with dementia d.t reversible cause (Endocrine, organ dysfunction, poly-pharmacy, stroke, infection .**

## CAM (confusion Assessment method)

| A(1) | I(2) | D(3) | C(4) |
|---|---|---|---|
| **Acute onset and fluctuating Course.** | **Inattention (easy distracted).** | **Disorganized thinking .** | **Alteration in conscious level episodes of drowsiness and agitations.** |

**Delirium = 1 & 2 + (3 or 4)**

## Agitation and confusion

Underlying causes of confusion need to be looked for and treated as appropriate, for example hypercalcemia, infection, urinary retention and medication. If specific treatments fail then the following may be tried:

- first choice: haloperidol
- other options: chlorpromazine, levomepromazine
- **Haloperidol 1-3 mg/8hrs. chlorpromazine 25-50 mg/8hrs. Or Metoclopramide + Chlorpromazine 10-25 / 8 hrs**

In the terminal phase of the illness then agitation or restlessness is best treated with midazolam

## Principles of pain killing and palliative care for terminally ill patients

### Morphine:

- Start by 5 mg every 4 hrs. if patient on weak analgesic. Increase up to 10 mg.
  Start by (10-20 mg) Q 4 hrs. if patient on strong analgesics.
- If from first dose patient is still in pain → next dose should INCREASE by 50%.
- Always use adjuvant analgesics.
- Usual dose is 20-60 mg/day.
- Must increase gradually until pain relief occur.
- It may be possible to omit overnight dose if double dose is given at bed time.
- When pain control achieved and dose is established? Total daily dose can be given as twice daily of long-acting preparations like "MST continus", "Zomorph.".
- Or Once daily "Mocap. SR " (usual dose 10-30 Q 12 hrs) **dose & not frequency should increase in case of analgesia not achieved.**
- Break though pain or activity cause pain like wound dressing needs a rescue dose = 1/6 of total daily dose.
- Switching to long-acting needs (4) hrs. interval from rapid acting Morphine.
  Parenteral dose: (diamorphine HCL).
  If patient became unable to swallow GIVE I.M dose = 1/2 oral solution (i.e., patient on 5 mg Q 4 hrs. can be given 2 mg Q 4 hrs)
  If on long acting then use 1/2 dose of long acting then divide Q hrs.

## Example:

- **patient on MST 30 mg x BD (total 60).**

Shift to IM: total dose = ½ divided every 4 hrs = 5mg Q 4hr.

**Transdermal route:**

- Morphine salt 90 mg = fentanyl "25"patch.
- Morphine salt 180 mg = fentanyl "50"patch.
- Morphine salt 270 mg = fentanyl "75"patch.
- Morphine salt 360 mg = fentanyl "100" patch.

Conversion between opioids

| From | To | Conversion factor |
|---|---|---|
| Oral codeine | Oral morphine | Divide by 10 |
| Oral tramadol | Oral morphine | Divide by 10** |

Oxycodone generally causes less sedation, vomiting and pruritis than morphine but more constipation.

| From | To | Conversion factor |
|---|---|---|
| Oral morphine | Oral oxycodone | Divide by 1.5-2*** |

The current BNF gives the following conversion factors for transdermal perparations

- a transdermal fentanyl 12 microgram patch equates to approximately 30 mg oral morphine daily
- a transdermal buprenorphine 10 microgram patch equates to approximately 24 mg oral morphine daily.

| From | To | Conversion factor |
|---|---|---|
| Oral morphine | Subcutaneous morphine | Divide by 2 |
| Oral morphine | Subcutaneous diamorphine | Divide by 3 |
| Oral oxycodone | Subcutaneous diamorphine | Divide by 1.5 |

## Reliefing Symptoms of Cancer

**GIT:** loperamide 2-4 mg Q 6 hrs OR hyoscine promide OR domperidone
**Bone pain:** Bisphosphonate, Radiotherapy, strontium
**Muscle spasm:** diazepam 5-10 mg/day or baclofen 5-10 mg/8hrs.
**Neuropathic pain:** TCA for several weeks or gabapentin tab.
**Nerve compression pain:** give dexamethasone 8 mg/day.
Reduce edema around the tumor and hence compression.
Nerve block & TENS are alternatives.

## Memory loss

In any patient presenting with cognitive impairment Assessment of reversable causes (delirium) must be made before diagnosing dementia

## Pressure ulcers

The following is based on a NHS Best Practice Statement. Please see the link for further details. Some selected points are listed below.
NICE also published guidelines .

Pressure ulcers develop in patients who are unable to move parts of their body due to illness, paralysis or advancing age.
They typically develop over bony prominences such as the sacrum or heel.
The following factors predispose to the development of pressure ulcers:

- malnourishment
- incontinence
- lack of mobility
- pain (leads to a reduction in mobility)

The **Waterlow score** is widely used to screen for patients who are at risk of developing pressure areas. It includes a number of factors including body mass index, nutritional status, skin type, mobility and continence.

Grading of pressure ulcers - the following is taken from the European Pressure Ulcer Advisory Panel classification system.

| Grade | Findings |
|---|---|
| **Grade 1** | Non-blanchable erythema of intact skin. Discolouration of the skin, warmth, oedema, induration or hardness may also be used as indicators, particularly on individuals with darker skin |
| **Grade 2** | Partial thickness skin loss involving epidermis or dermis, or both. The ulcer is superficial and presents clinically as an abrasion or blister |
| **Grade 3** | Full thickness skin loss involving damage to or necrosis of subcutaneous tissue that may extend down to, but not through, underlying fascia. |
| **Grade 4** | Extensive destruction, tissue necrosis, or damage to muscle, bone or supporting structures with or without full thickness skin loss |

### Management

- a moist wound environment encourages ulcer healing. Hydrocolloid dressings and hydrogels may help facilitate this. The use of soap should be discouraged to avoid drying the wound
- wound swabs should not be done routinely as the vast majority of pressure ulcers are colonized with bacteria. The decision to use systemic antibiotics should be taken on a clinical basis (e.g. Evidence of surrounding cellulitis)
- consider referral to the tissue viability nurse
- surgical debridement may be beneficial for selected wounds

## Raised I.C. pressure

- **Headache:** Dexamethasone 16 mg/day = for 4-5 days then reduce to 4-6 mg/day.
  Should be given before 6 pm to reduce insomnia.
- **Intractable cough:**
  **Moist inhalation.**
  **Regular administration Of morphine (5 mg / 4 hrs)**
- **Dyspnea: morphine 5 mg /4 hrs or diazepam 5-10 mg daily.**
  **Dexamethazone 4-8 mg/day if there is Bronchospasm.**

## Hiccups

### Management of hiccups

- chlorpromazine is licensed for the treatment of intractable hiccups
- haloperidol, gabapentin are also used
- dexamethasone is also used, particularly if there are hepatic lesions

## Syringe Drivers

A syringe driver should be considered in the palliative care setting when a patient is unable to take oral medication due to nausea, dysphagia, intestinal obstruction, weakness or coma. In the UK there are two main types of syringe driver:

- Graseby MS16A (blue): the delivery rate is given in mm per hour
- Graseby MS26 (green): the delivery rate is given in mm per 24 hours

The majority of drugs are compatible with water for injection although for the following drugs sodium chloride 0.9% is recommended:

- granisetron
- ketamine
- ketorolac
- octreotide
- ondansetron

## Commonly used drugs

- nausea and vomiting: cyclizine, levomepromazine, haloperidol, metoclopramide
- **respiratory secretions/bowel colic:** hyoscine hydrobromide, hyoscine butylbromide, or glycopyrronium bromide.
- agitation/restlessness: midazolam, haloperidol, levomepromazine
- pain: diamorphine is the preferred opioid

## Mixing and compatibility issues

- diamorphine is compatible with the majority of other drugs used including dexamethasone, haloperidol, hyoscine butylbromide, hyoscine hydrobromide, levomepromazine, metoclopramide, midazolam
  - cyclizine may precipitate with diamorphine when given at higher doses
- cyclizine is incompatible with a number of drugs including clonidine, dexamethasone, hyoscine butylbromide (occasional), ketamine, ketorolac, metoclopramide, midazolam, octreotide, sodium chloride 0.9%

# Pharmaceuticals & Therapeutics

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# Basics of Pharmacology

## Pharmacokinetics: metabolism

Drug metabolism usually involves two types of biochemical reactions - phase I and phase II reactions:

- Phase I reactions: oxidation, reduction, and hydrolysis. Mainly performed by the P450 enzymes but some drugs are metabolised by specific enzymes, for example **alcohol dehydrogenase** and **xanthine oxidase**. Products of phase I reactions are typically **more active** and **potentially toxic.**
- Phase II reactions: conjugation. Products are typically **inactive** and **excreted in urine or bile**. Glucuronyl, acetyl, methyl, sulphate and other groups are typically involved.

**Drug metabolism:**

- Phase I: **Oxidation, Reduction, Hydrolysis**
- Phase II: **Conjugation**

The majority of phase I and phase II reactions take place in the **liver.**
Usually products of both phase I and II reactions **are less lipid solubility.**

### Clearance:

- majority of drugs exhibit 'first-order' elimination kinetics i.e. the rate of drug elimination is proportional to drug concentration
- certain drugs exhibit zero-order kinetics where the rate of excretion is constant despite changes in plasma concentration, this is due to saturation of the metabolic process
- examples of drugs exhibiting zero-order kinetics include **phenytoin and salicylates**

### First-pass metabolism:

This is a phenomenon where the concentration of a drug is greatly reduced before it reaches the systemic circulation due to hepatic metabolism.

As a consequence much larger doses are need orally than if given by other routes. This effect is seen in many drugs, including:

- **Aspirin**
- **Isosorbide dinitrate**
- **GTN** Glyceryl trinitrate
- **Lignocaine**
- **Propranolol**
- **Verapamil**
- **Isoprenaline**
- **Testosterone**
- **Hydrocortisone**

Questions concerning zero-order kinetics and acetylator status are also common in the exam.

## Zero-order saturation pharmacokinetics:

Zero-order kinetics describes metabolism which is independent of the concentration of the reactant.

This is due to **metabolic pathways becoming saturated** resulting in a **constant amount** of drug being **eliminated** per **unit time**.

This explains why people may fail a breathalyser test in the morning if they have been drinking the night before.

### Drugs exhibiting zero-order kinetics:

- **Ethanol**
- **Phenytoin**
- Salicylates (e.g. high-dose aspirin)
- Heparin
- Warfarin
- Theophylline

## Acetylator status:

**50%** of the UK population are deficient in hepatic N-acetyltransferase.

### Drugs affected by acetylator status:

- **Isoniazid (INH)**
- **Hydralazine**
- **P**rocainamide
- Dapsone
- Sulfasalazine

It was previously thought that 'fast acetylators' were more at risk of isoniazid than other patients. Recent research now suggests however that **slow acetylators** are actually more likely to suffer hepatotoxicity.

**Fast acetylation** leads to **higher** blood levels of the **toxic metabolite** acetyl isoniazid and thus to an increase risk of **toxic hepatitis** which is 250 times more common than in slow acetylators.

**Slow acetylators**, on the other hand, may be associated adverse effects secondary to **higher drug concentrations**, which can lead to **peripheral neuropathy**.

# P450 enzyme system

Induction usually requires prolonged exposure to the inducing drug, as opposed to P450 inhibitors, where effects are often seen rapidly.

| Inducers | Inhibitors |
|---|---|
| • **Rifampicin**<br>• Antiepileptics:<br>  ○ **Phenytoin**,<br>  ○ **Carbamazepine**<br>  ○ Barbiturates: Phenobarbitone<br>• **Griseofulvin**<br>• Smoking<br>• **St John's Wort**<br>• **Chronic** alcohol intake<br>• Quinidine.<br>• Tetracycline<br>• Nevirapine (NNRTI) | • **Isoniazid (INH).**<br>• Antibiotics:<br>  ○ **Ciprofloxacin / Levo,**<br>  ○ **Erythromycin / Clarith**<br>  ○ **Co-trimoxazole.**<br>• Quinupristin & Dalfopristin ABx.<br>• Sodium **valproate (Depakin)**<br>• **SSRIs**: fluoxetine, sertraline<br>• **SNRIs**: Venlafaxine<br>• **Cimetidine, Omeprazole**<br>• **Amiodarone**<br>• **Deltiazem & Verapamil**<br>• Allopurinol<br>• **Ketoconazole, fluconazole**<br>• **Metronidazole**<br>• **Acute** alcohol intake<br>• **Cranberry juice**<br>• **Grapefruit juice**<br>• **Methylprednisolone** (high dose)<br>• **UDCA (ursofalk)**<br>• Ritonavir (PI) |

The most important drugs that are affected by the P450 enzyme system:

- **Warfarin**
- **Amiodarone**
- **Digoxin**
- **Statins**
- **Combined oral contraceptive pill**
- **Phenytoin**
- **Cyclosporine**
- **Aminophylline**

**Enzyme inducer** → **induce** CYP1A2 isoenzyme, so **reducing** the effectiveness of the above mentioned drugs.

**Enzyme inhibitor** → **inhibit** CYP1A2 isoenzyme, so **increased** the effectiveness of the above mentioned drugs (↑ its levels → Toxicity).

Smoking affects **CYP1A2**, so that why smokers require more aminophylline.

Carbamazepine is an inducer of the P450 system. This in turn increases the metabolism of carbamazepine itself - auto-induction.

**Grapefruit juice** is potent **inhibitor** of the cytochrome P450 enzyme CYP3A4

Concomitant use of **atorvastatin** and **large amounts of grapefruit juice** should be avoided as it contributed to ↑ **statin-associated myotoxicity**

Multiple studies have demonstrated this interaction between **grapefruit juice** and **felodipine**. Felodipine is normally metabolised in the GI tract and liver by CYP3A4. Grapefruit juice contains bergamottin which INHIBITS CYP3A4, thereby **increasing the bioavailability of felodipine** and the risk of toxicity with **increase postural hypotension** especially in old patient.

A raised INR is a result of **inhibited** liver enzymes.

**Co-enzyme Q10** is similar to **Vit. K** and reduces warfarin's anticoagulant effect

**HIV TTT: HAART - P450 interaction**:
- Nevirapine (a NNRTI): **induces** P450.
- Protease inhibitors (PI) like Ritonavir: **inhibits** P450.

## P450 drug interactions: more detail

Whilst you are expected to know in broad terms what are the main inhibitors and inducers of the P450 system it is unlikely that you will be asked detailed questions about the individual enzyme systems.

It is worthwhile noting that the **most important** and **common reason** for drug interactions is the **P450 CYP3A4 system**.

The table below shows the main enzyme systems that are affected by common drugs. There is clearly a lot of overlap within the various P450 enzymes.

| P450 system | Substrates | Inducers | Inhibitors |
|---|---|---|---|
| **CYP3A4** | Macrolides.<br>Antiretrovirals.<br>CCBs. | Carbamazepine.<br>Phenytoin.<br>Phenobarbitone.<br>Rifampicin.<br>St John's Wort. | Macrolides.<br>Protease inhibitors (including ritonavir).<br>Imidazoles. |
| CYP2D6 | TCA.<br>Antipsychotics. | | SSRIs<br>Ritonavir |
| **CYP2C9** | **Warfarin.**<br>Sulfonylureas. | Rifampicin | Imidazoles<br>Amiodarone<br>Sodium valproate |
| CYP1A2 | Theophylline | Smoking<br>Omeprazole | Ciprofloxacin |
| CYP2E1 | Alcohol | Chronic alcohol<br>Isoniazid | |

A 69-year-old man is started on warfarin dt atrial fibrillation. During warfarin loading it is noted that his INR rises much more rapidly than expected. Genetic variation in which P450 enzyme systems is most likely to explain this>> **CYP2C9. Warfarin is a substrate of CYP2C9.**

## Pharmacodynamics

- Pharmacodynamics is often considered to be 'what the drugs do to the body' (in contrast to pharmacokinetics which is concerned with 'what the body does to the drugs').
- It is obviously a vast topic, so the text below is an introduction to some key concepts.
- Classically drugs exert their effect via interaction with a target, commonly (but not always) a protein.
- Targets may be intracellular or extracellular and can be a cellular receptor on the cell membrane, an intracellular receptor exerting an effect on the nucleus, an enzyme, transport proteins or even a specific nucleic acid sequence.

**Within the cellular targets, there are 4 main types:**

- **Ion channels-** These are the simplest form of receptor, once the drug binds to a receptor on this target the channel is either opened or closed dependent upon the action of the drug and whether it is an agonist or antagonist (see below). Examples of drugs working on ion channels include most local anaesthetics (e.g. lidocaine) that work on voltage-gated sodium channels.
- **G-protein coupled receptors (GPCRs)-** These are more complex than ion channels. When the drug binds to the target, it causes a sequence of events within the G-protein subunits which then leads to production of a secondary messenger such as cyclic AMP or a protein phosphorylation cascade. These second messengers are actually responsible for causing the effect. Adrenoreceptors are an example of G-protein coupled receptors.
- **Tyrosine kinase receptors-** these receptors are different in their mechanism to both ion channels and GPCRs. When a drug activates a tyrosine kinase receptor it leads to a series of steps within the cell, normally involving phosphorylation of targets, then causing effects which often include cell growth and differentiation. Insulin is a commonly used drug (as well as endogenous hormone!) that works via a tyrosine kinase receptor.
- **Nuclear receptors-** As the name suggests these receptors are located within the nucleus of the cell and activation or inhibition of these receptors typically causes increased or decreased gene transcription. Drugs interacting with these receptors must obviously be lipid-soluble in order to penetrate the cell membrane, after which it forms a complex with a receptor protein before exerting an effect. Commonly used drugs that work via this route are steroids such as prednisolone and other hormone replacements such as levothyroxine.

With all different receptor targets, it is also important to consider whether the drug has a 'positive' or 'negative' impact on the receptor.

- **Agonists are drugs which activates the receptor.**
- **Antagonists are those which block a receptor** preventing activation, it is important to note they do not deactivate a receptor.

Antagonists may be competitive or non-competitive. A competitive antagonist binds at the same site as an agonist, thereby occupying it and preventing an agonist occupying the site.

A non-competitive antagonist occupies another site which often causes a conformational change in the binding site where an agonist would otherwise bind.

- **'Binding affinity'** is a concept of how readily a drug will bind to the specific receptor, in most cases the more receptors that are occupied by a drug, the greater the effect produced.
- **'Efficacy'** is the measure of how able an agonist is to produce a response once it has bound to the receptor.
- **'Potency'** is related to the concentration at which a drug is effective.
- **'Therapeutic Index'** is the ratio of the dose of a drug resulting in an undesired effect compared to that at which it produces the desired effect. Calculation of a therapeutic index is complex, however, it is sufficient to be aware of certain drugs with a 'narrow therapeutic index', such as the antibiotic gentamicin which whilst effective, requires close monitoring to avoid adverse effects.

### Dose-response relationship

- The relationship between the amount of drug given (dose) and the impact it has on the patient (response) is very rarely entirely linear. Often drugs that work by occupying a certain receptor may 'saturate' the available receptors and so further increased doses will not cause any more response.
- Many drugs do not start to have a significant impact below a certain dose and so are considered to be 'sub-therapeutic' below such a dose.
- The relationship between dose and response can be well illustrated on dose-response graphs with the dose on the x-axis and response on the y-axis; such graphs allow easy comparison of the characteristics of different drugs. It is, of course, important to remember that dose-response also varies between individuals.

## Therapeutic drug monitoring

### Lithium

- range = 0.4 - 1.0 mmol/l
- take 12 hrs. post-dose.

**Ciclosporin:** trough levels immediately before dose

**Digoxin:** at least 6 hrs post-dose

Phenytoin levels do not need to be monitored routinely but **trough levels, immediately before dose** should be checked if:

- adjustment of phenytoin dose
- suspected toxicity
- detection of non-adherence to the prescribed medication

# Drug monitoring

The tables below show the monitoring requirements of common drugs. It should be noted these are basic guidelines and do not relate to monitoring effectiveness of treatment (e.g. Checking lipids for patients taking a stati

## Cardiovascular drugs

| Drug | Main monitoring parameters | Details of monitoring |
|---|---|---|
| Statins | LFT | LFTs at baseline, 3 months and 12 months |
| ACE inhibitors | U&E | U&E prior to treatment<br>U&E after increasing dose<br>U&E at least annually |
| Amiodarone | TFT, LFT | TFT, LFT, U&E, CXR prior to treatment<br>TFT, LFT every 6 months |

# Adrenoceptors

**Alpha-1**

- vasoconstriction
- relaxation of GI smooth muscle
- salivary secretion
- hepatic glycogenolysis

**Alpha-2**

- mainly presynaptic: inhibition of transmitter release (inc NA, Ach from autonomic nerves)
- inhibits insulin
- platelet aggregation

**Beta-1**

- mainly located in the heart
- increase heart rate + force

**Beta-2**

- vasodilation
- relaxation of GI smooth muscle
- bronchodilation

**Beta-3:** lipolysis

**Pathways**

- all are G-protein coupled
- alpha-1: activate phospholipase C → IP3 → DAG
- alpha-2: inhibit adenylate cyclase
- beta-1: stimulate adenylate cyclase
- beta-2: stimulate adenylate cyclase
- beta-3: stimulate adenylate cyclase

## Adrenoceptor agonists

**Alpha-1 agonists:** phenylephrine
**Alpha-2 agonists:** clonidine
**Beta-1 agonists:** dobutamine
**Beta-2 agonists:** salbutamol
**Beta-3 agonists:** being developed, may have a role in preventing obesity (stimulation causes lipolysis), used in overactive bladder treatment.

## Adrenoceptor antagonists

**Alpha antagonists**

- **alpha-1**: doxazosin
- **alpha-1a**: tamsulosin - acts mainly on urogenital tract
- **alpha-2**: yohimbine
- non-selective: phenoxybenzamine (previously used in peripheral arterial disease)

**Beta antagonists**

- beta-1: atenolol
- non-selective: propranolol

Carvedilol and labetalol are mixed alpha and beta antagonists

## Dopamine receptor agonists

### Indications

- Parkinson's disease
- prolactinoma/galactorrhoea
- cyclical breast disease
- acromegaly

Currently accepted practice in the management of patients with Parkinson's disease is to delay treatment until the onset of disabling symptoms and then to introduce a dopamine receptor agonist. If the patient is elderly, L-dopa is sometimes used as an initial treatment

### Overview

- e.g. bromocriptine, ropinirole, cabergoline, apomorphine ergot-derived dopamine receptor agonists (bromocriptine, cabergoline, pergolide*) have been associated with **pulmonary, retroperitoneal and cardiac fibrosis**.
- The Committee on Safety of Medicines advice that an ESR, creatinine and chest x-ray should be obtained prior to treatment and patients should be closely monitored

## Adverse effects

- nausea/vomiting
- postural hypotension
- hallucinations
- daytime somnolence

***pergolide was withdrawn from the US market in March 2007 due to concern regarding increased incidence of valvular dysfunction**

# Drugs which act on serotonin receptors (5HT)

Below is a summary of drugs which are known to act via modulation of the **serotonin (5-HT) system.**

## Agonists:

- **Sumatriptan** is a 5-HT1D receptor agonist which is used in the **acute** treatment of migraine.
- **Ergotamine** is a partial agonist of 5-HT1 receptors.

## Antagonists:

- **Pizotifen** is a 5-HT2 receptor antagonist used in the **prophylaxis** of migraine attacks.
- **Methysergide** is another antagonist of the 5-HT2 receptor but is rarely used due to the risk of retroperitoneal fibrosis.
- **Cyproheptadine** is a 5-HT2 receptor antagonist which is used to control diarrhoea in patients with carcinoid syndrome.
- **Ondansetron and Granisetron** are a **5-HT3** receptor antagonist and is used as an antiemetic. The most common SE is **Constipation**.

It should be noted that 5-HT receptor agonists are used in the acute treatment of migraine whilst 5-HT receptor antagonists are used in prophylaxis.

# Drugs acting on common receptors

The table below lists the common receptors and gives examples of both agonists and antagonists. It is not comprehensive and is intended to give examples of each.

| Receptor | Agonist | Antagonist |
|---|---|---|
| **Alpha** | Alpha-1: Decongestants (e.g. phenylephrine/oxymetazoline)<br>Alpha-2: Glaucoma (e.g. topical brimonidine) | Benign prostatic hyperplasia (e.g. tamsulosin)<br>Hypertension (e.g. doxazosin) |
| **Beta-1** | Inotropes (e.g. dobutamine) | Non-selective & selective beta-blockers (e.g. atenolol, bisoprolol) |
| **Beta-2** | Bronchodilators (e.g. salbutamol) | Non-selective beta-blockers (e.g. propranolol, labetalol) |
| **Dopamine** | Parkinson's disease (e.g. ropinirole)<br>Prolactinoma | Schizophrenia (antipsychotics e.g. haloperidol)<br>Anti-emetics (e.g. metoclopramide/domperidone) |
| **GABA** | Benzodiazepines<br>Baclofen | Flumazenil |
| **Histamine-1** | | Antihistamines (e.g. loratadine) |
| **Histamine-2** | | Antacids (e.g. ranitidine) |
| **Muscarinic** | Glaucoma (e.g. pilocarpine) | Atropine (e.g. for bradycardia)<br>Bronchodilator (e.g. ipratropium bromide, tiotropium)<br>Urge incontinence (e.g. oxybutynin) |
| **Nicotinic** | Nicotine<br>Varenicline (used for smoking cessation)<br>Depolarising muscle relaxant (e.g. suxamethonium) | Non-depolarising muscle relaxants (e.g. atracurium) |
| **Oxytocin** | Inducing labour (e.g. Syntocinon) | Tocolysis (e.g. atosiban) |
| **Serotonin** | Triptans (for acute migraine, e.g. zolmitriptan) | Anti-emetics (e.g. ondansetron) |

# Important drugs

## Anaesthetic agents

**The table below summarizes some of the more commonly used IV induction agents**

| Agent | Specific features |
|---|---|
| **Propofol** | • GABA receptor agonist<br>• Rapid onset of anaesthesia<br>• Pain on IV injection<br>• Rapidly metabolised with little accumulation of metabolites<br>• Proven anti emetic properties<br>• Moderate myocardial depression<br>• Widely used especially for maintaining sedation on ITU, total IV anaesthesia and for daycase surgery |
| **Sodium thiopentone** | • Extremely rapid onset of action making it the agent of choice for rapid sequence of induction<br>• Marked myocardial depression may occur<br>• Metabolites build up quickly<br>• Unsuitable for maintenance infusion<br>• Little analgesic effects |
| **Ketamine** | • **NMDA receptor antagonist**<br>• May be used for induction of anaesthesia<br>• Has moderate to strong analgesic properties<br>• Produces little myocardial depression making it a suitable agent for anaesthesia in those who are haemodynamically unstable<br>• May induce state of dissociative anaesthesia resulting in nightmares |
| **Etomidate** | • Has favorable cardiac safety profile with very little haemodynamic instability<br>• No analgesic properties<br>• Unsuitable for maintaining sedation as prolonged (and even brief) use may result in adrenal suppression<br>• Post operative vomiting is common |

# Local anesthetic agents

## Lidocaine

- An amide
- Local anaesthetic and a less commonly used antiarrhythmic (affects Na channels in the axon)
- Hepatic metabolism, protein bound, renally excreted
- Toxicity: due to IV or excess administration. Increased risk if liver dysfunction or low protein states. Note acidosis causes lidocaine to detach from protein binding. **Local anesthetic toxicity can be treated with IV 20% lipid emulsion**
- Drug interactions: Beta blockers, ciprofloxacin, phenytoin
- Features of toxicity: Initial CNS over activity then depression as lidocaine initially blocks inhibitory pathways then blocks both inhibitory and activating pathways. Cardiac arrhythmias.
- Increased doses may be used when combined with adrenaline to limit systemic absorption.

## Cocaine

- Pure cocaine is a salt, usually cocaine hydrochloride. It is supplied for local anaesthetic purposes as a paste.
- It is supplied for clinical use in concentrations of 4 and 10%. It may be applied topically to the nasal mucosa. It has a rapid onset of action and has the additional advantage of causing marked vasoconstriction.
- It is lipophillic and will readily cross the blood brain barrier. Its systemic effects also include cardiac arrhythmias and tachycardia.
- Apart from its limited use in ENT surgery it is otherwise used rarely in mainstream surgical practice.

## Bupivacaine

- Bupivacaine binds to the intracellular portion of sodium channels and blocks sodium influx into nerve cells, which prevents depolarization.
- It has a much longer duration of action than lignocaine and this is of use in that it may be used for topical wound infiltration at the conclusion of surgical procedures with long duration analgesic effect.
- It is cardiotoxic and is therefore contra indicated in regional blockage in case the tourniquet fails.
- Levobupivacaine (Chirocaine) is less cardiotoxic and causes less vasodilation.

**Prilocaine:** Similar mechanism of action to other local anesthetic agents. However, it is far less cardiotoxic and is therefore the agent of choice for intravenous regional anesthesia e.g., Biers Block.

All local anesthetic agents dissociate in tissues and this contributes to their therapeutic effect. The dissociation constant shifts in tissues that are acidic e.g., where an abscess is present, and this reduces the efficacy.

**Doses of local anaesthetics**

| Agent | Dose plain | Dose with adrenaline |
|---|---|---|
| Lignocaine | 3mg/Kg | 7mg/Kg |
| Bupivacaine | 2mg/Kg | 2mg/Kg |
| Prilocaine | 6mg/Kg | 9mg/Kg |

These are a guide only as actual doses depend on site of administration, tissue vascularity and co-morbidities.

**Maximum total local anaesthetic doses**

Lignocaine 1% plain - 3mg/ Kg - 200mg (20ml)

- Lignocaine 1% with 1 in 200,000 adrenaline - 7mg/Kg - 500mg (50ml)
- Bupivicaine 0.5% - 2mg/kg- 150mg (30ml)

*Maximum doses are based on ideal body weight*

## Antibiotics: gross mechanism of action

The diagram and list below summarises the gross mechanism of action of the commonly used antibiotics. More detailed descriptions are found elsewhere on the site.

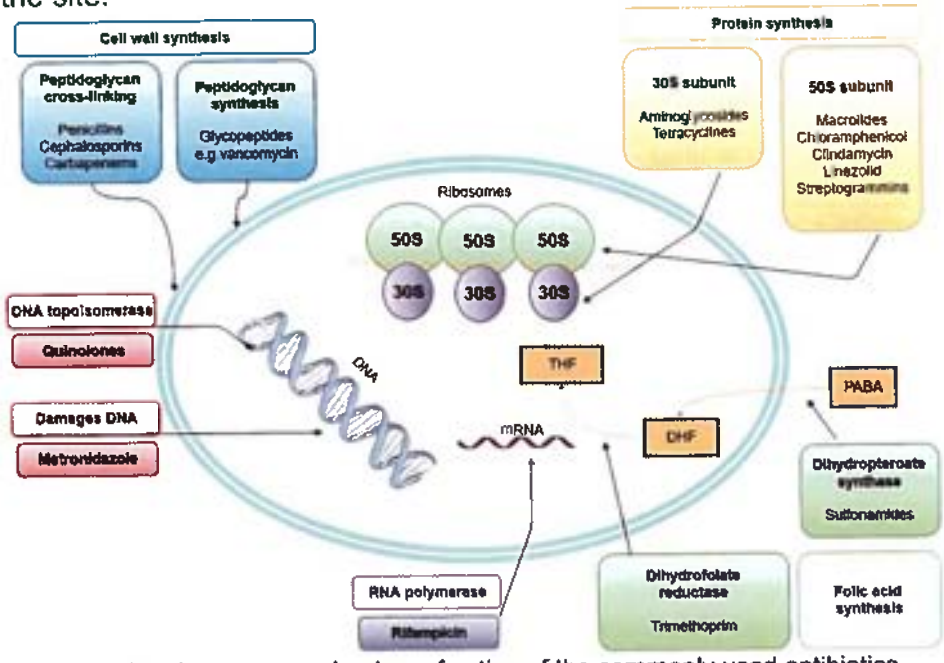



Diagram showing the gross mechanism of action of the commonly used antibiotics

**Inhibits cell wall formation**
- peptidoglycan cross-linking: penicillins, cephalosporins, carbopenems
- peptidoglycan synthesis: glycopeptides (e.g. vancomycin)

**Inhibits protein synthesis (by acting on the ribosome)**
- 50S subunit: macrolides, chloramphenicol, clindamycin, linezolid, streptogrammins
- 30S subunit: aminoglycosides, tetracyclines

**Inhibits DNA synthesis**
- quinolones (e.g. ciprofloxacin)

**Damages DNA**
- metronidazole

**Inhibits folic acid formation**
- sulphonamides
- trimethoprim

**Inhibits RNA synthesis**
- rifampicin

## Antibiotic guidelines

The following is based on current BNF guidelines:

## Respiratory system:

| Condition | Recommended treatment |
|---|---|
| Exacerbations of chronic bronchitis | Amoxicillin or tetracycline or clarithromycin |
| Uncomplicated community-acquired pneumonia | Amoxicillin (Doxycycline or clarithromycin in penicillin allergic, add flucloxacillin if staphylococci suspected e.g. In influenza) |
| Pneumonia possibly caused by **atypical** pathogens | Clarithromycin |
| Hospital-acquired pneumonia (**HAP**) | ➢ Within 5 days of admission: co-amoxiclav or cefuroxime.<br>➢ More than 5 days after admission:<br>o Piperacillin with tazobactam.<br>o OR a broad-spectrum cephalosporin (e.g. ceftazidime).<br>o OR a quinolone (e.g. ciprofloxacin). |

## Urinary tract:

| Condition | Recommended treatment |
|---|---|
| Lower urinary tract infection | Trimethoprim or nitrofurantoin. Alternative: amoxicillin or cephalosporin |
| Acute pyelonephritis | Broad-spectrum cephalosporin or quinolone |
| Acute prostatitis | Quinolone or trimethoprim |

## Skin:

| Condition | Recommended treatment |
|---|---|
| Impetigo | Topical fusidic acid, oral flucloxacillin or erythromycin if widespread |
| Cellulitis | Flucloxacillin (clarithromycin or clindomycin if penicillin-allergic) |
| Erysipelas | Phenoxymethylpenicillin (erythromycin if penicillin-allergic) |
| **Animal** or **human** bite | **Co-amoxiclav** (Doxycycline + Metronidazole or Clarithromycin + Metronidazole if penicillin-allergic) |

## Ear, nose & throat:

| Condition | Recommended treatment |
|---|---|
| Throat infections | Phenoxymethylpenicillin (erythromycin alone if penicillin-allergic) |
| Sinusitis | Amoxicillin or doxycycline or erythromycin |
| Otitis media | Amoxicillin (erythromycin if penicillin-allergic) |
| Otitis externa* | Flucloxacillin (erythromycin if penicillin-allergic) |

## Genital system:

| Condition | Recommended treatment |
|---|---|
| Gonorrhoea | Cefixime or ciprofloxacin** |
| Chlamydia | Doxycycline or azithromycin |
| Pelvic inflammatory disease | Oral ofloxacin + oral metronidazole or intramuscular ceftriaxone + oral doxycycline + oral metronidazole |
| Syphilis | Benzathine benzylpenicillin or doxycycline or erythromycin |
| Bacterial vaginosis | Oral or topical metronidazole or topical clindamycin |

* A combined topical antibiotic and corticosteroid is generally used for mild/moderate cases of otitis externa

** There is actually now significant resistance to ciprofloxacin and other guidelines recommend Cefixime 400mg PO (single dose) or ceftriaxone 250mg IM.

## Summary of antibiotics action, classification and uses

| Inhibit | | Classification | | Antibiotics |
|---|---|---|---|---|
| Cell Wall Synthesis | Beta Lactams | Penicillins | Natural Penicillins | Penicillin G; Penicillin V; Procaine Penicillin G; Benzathine Penicillin G |
| | | | Antistaphylococcal Penicillins | Methicillin; Nafcillin; Oxacillin; Cloxacillin; Dicloxacillin; Flucloxacillin |
| | | | Aminopenicillins | Ampicillin; Amoxicilin |
| | | | Broad Spectrum Penicillins | Ampicillin/Sulbactam; Sultamicillin; Co-Amoxiclav (Amoxicillin/Clavulanate) |
| | | | Anti-Pseudomonal Penicillins | Carboxypenicillins: Ticarcillin; Carbenicillin<br>Ureidopenicillins: Piperacillin; Mezlocillin; Azlocillin<br>Combination: Ticarcillin/Clavulanate; Piperacillin/Tazobactam |
| | | Cephalosporins | 1st Generation | Cefadroxil; Cephalaxin; Cephradine; Cefazolin |
| | | | 2nd Generation | Cefaclor; Cefuroxime; Cefprozil; Cefoxitin |
| | | | 3rd Generation | Ceftriaxone; Cefotaxime; Cefoperazone; Ceftazidime; Ceftazidime/Avibactam; Cefixime; Cefdinir; Cefpodoxime; Cefditoren |
| | | | 4th Generation | Cefepime; Cefpirome |
| | | | 5th Generation | Ceftobiprole; Ceftaroline; Ceftolozane/Tazobactam |
| | | Monobactams | | Aztreonam |
| | | Carbapenems | | Imipenem/Cilastatin; Meropenem; Doripenem; Ertapenem |
| | Non-β-lactams | Glycopeptide Antibiotics | | Vancomycin; Teicoplanin; Telavancin; Dalbavancin; Oritavancin |
| | | Others | | Fosfomycin; Bacitracin; Cycloserine |
| Cell Membrane | | | | Colistin; Daptomycin |
| Protein Synthesis | 30S | Tetracyclines | | Tetracycline; Oxytetracycline; Doxycycline; Minocycline |
| | | Glycylcyclines | | Tigecycline |
| | | Aminoglycosides | | Streptomycin; Neomycin; Amikacin; Gentamicin; Tobramycin |
| | 50S | Macrolides | | Erythromycin; Clarithromycin; Azithromycin; Spiramycin; Josamycin |
| | | Ketolides | | Telithromycin |
| | | Macrocyclic | | Fidaxomicin |
| | | Chloramphenicol | | Chloramphenicol |
| | | Oxazolidinones | | Linezolid; Tedizolid |
| | | Lincosamides | | Clindamycin |
| | | Streptogramins | | Quinupristin/Dalfopristin; Pristinamycin |
| | Others | | | Fusidic Acid; Rifaximin; Retapamulin; Plazomicin; Mupirocin |
| Nucleic Acid Synthesis | DNA Topoisomerases | Quinolones | | Nalidixic acid; Cinoxacin |
| | | Fluoro quinolones | Second | Ciprofloxacin; Norfloxacin; Ofloxacin; Enoxacin; Lomefloxacin; Pefloxacin |
| | | | Third | Levofloxacin; Sparfloxacin; Grepafloxacin |
| | | | Fourth | Trovafloxacin; Moxifloxacin; Gatifloxacin; Gemifloxacin |
| | Antifolates | Sulfonamides | | Sulfamethoxazole; Sulfadiazine; Silver Sulfadiazine; Sulfadoxine; Mafenide; Sulfacetamide |
| | | DHFR inhibitor | | Trimethoprim; Pyrimethamine |
| | | CO | | Co-Trimoxazole; Sulfadoxine/Pyrimethamine |

## Macrolides

Erythromycin was the first macrolide used clinically. Newer examples include clarithromycin and azithromycin.

Macrolides act by inhibiting bacterial protein synthesis by blocking translocation. If pushed to give an answer they are bacteriostatic in nature, but in reality this depends on the dose and type of organism being treated.

### Mechanism of resistance

- post-transcriptional methylation of the 23S bacterial ribosomal RNA

### Adverse effects

- prolongation of the QT interval
- gastrointestinal side-effects are common. Nausea is less common with clarithromycin than erythromycin
- cholestatic jaundice: risk may be reduced if erythromycin stearate is used
- P450 inhibitor (see below)
- azithromycin is associated with hearing loss and tinnitus

**Common interactions:** statins should be stopped whilst taking a course of macrolides. Macrolides inhibit the cytochrome P450 isoenzyme CYP3A4 that metabolizes statins. Taking macrolides concurrently with statins significantly increases the risk of myopathy and rhabdomyolysis.

## Quinolones

Quinolones are a group of antibiotics which work by inhibiting DNA synthesis and are bactericidal in nature. Examples include:

- ciprofloxacin
- levofloxacin

**Mechanism of action:** inhibit topoisomerase II (DNA gyrase) and topoisomerase IV

**Mechanism of resistance:** mutations to DNA gyrase, efflux pumps which reduce intracellular quinolone concentration

### Adverse effects

- **lower seizure threshold** in patients with epilepsy
- **tendon damage** (including rupture) - the risk is increased in patients also taking steroids
- cartilage damage has been demonstrated in animal models and for this reason quinolones are generally avoided (but not necessarily contraindicated) in children
- **lengthens QT interval**

### Contraindications

- Quinolones should generally be avoided in women who are pregnant **or breastfeeding**
- avoid in **G6PD**

## Gentamicin

Gentamicin is a type of aminoglycoside antibiotic. It is poorly lipid-soluble and is therefore given parentally (e.g. for infective endocarditis) or topically (e.g. for otitis externa).

### Adverse effects

- ototoxicity
  - due to auditory or vestibular nerve damage
  - irreversible
- nephrotoxicity
  - accumulates in renal failure
  - the toxicity is secondary to **acute tubular necrosis**
  - concomitant use of furosemide increases the risk
  - lower doses and more frequent monitoring is required

### Contraindications

- myasthenia gravis

### Dosing

- due to the significant ototoxic and nephrotoxic potential of gentamicin it is important to monitor plasma concentrations
- both peak (1 hour after administration) and trough levels (just before the next dose) are measured
- if the trough (pre-dose) level is high the interval between the doses should be increased if the peak (post-dose) level is high the dose should be decreased

## Tuberculosis: drug side-effects and mechanism of action

### Rifampicin

- mechanism of action: inhibits bacterial DNA dependent RNA polymerase preventing transcription of DNA into mRNA
- potent liver enzyme inducer
- **hepatitis**, orange secretions
- flu-like symptoms

## Isoniazid

- mechanism of action: inhibits mycolic acid synthesis
- **peripheral neuropathy**: prevent with pyridoxine (Vitamin B6)
- hepatitis, agranulocytosis
- liver enzyme inhibitor

## Pyrazinamide

- mechanism of action: converted by pyrazinamidase into pyrazinoic acid which in turn inhibits fatty acid synthase (FAS) I
- hyperuricaemia causing **gout**
- arthralgia, myalgia
- hepatitis

## Ethambutol

- mechanism of action: inhibits the enzyme arabinosyl transferase which polymerizes arabinose into arabinan
- **optic neuritis**: check visual acuity before and during treatment

**dose needs adjusting in patients with renal impairment.**

## Drug-induced pancytopenia (see hematology)

- Cytotoxics.
- Antibiotics: Trimethoprim, Chloramphenicol.
- Anti-rheumatoid: Gold and Penicillamine.
- **Carb**imazole (It causes both agranulocytosis and pancytopaenia)
- Anti-epileptics: Phenytoin and **Carb**amazepine.
- Sulphonylurea: tolbutamide.

## Drug causes of agranulocytosis (see hematology)

**Common drugs that cause agranulocytosis:**

- Antithyroid drugs - carbimazole, propylthiouracil
- Antipsychotics - atypical antipsychotics (CLOZAPINE)
- Antiepileptics - **carbamazepine**
- Antibiotics - penicillin, chloramphenicol, co-trimoxazole
- Antidepressant - mirtazapine
- Cytotoxic drugs – methotrexate

## Drug-induced urinary retention

**The following drugs may cause urinary retention:**

- **tricyclic antidepressants e.g. amitriptyline**
- anticholinergics e.g. antipsychotics, antihistamines
- opioids
- NSAIDs
- disopyramide

## Drugs cause Gingival hyperplasia

**cause of gingival hyperplasia:**

- **Phenytoin.**
- **Cyclosporine.**
- **Calcium channel blockers** (especially **Nifedipine**).

**Other causes of gingival hyperplasia include:**

- **AML** acute myeloid leukaemia (myelomonocytic and monocytic types).

Gingival hyperplasia >>>> Phenytoin, Cyclosporine, CCBs and AML

## Drugs causing lung fibrosis

**Causes**

- amiodarone
- cytotoxic agents: busulphan, bleomycin
- anti-rheumatoid drugs: methotrexate, sulfasalazine
- **nitrofurantoin**
- **ergot-derived dopamine receptor agonists (bromocriptine, cabergoline, pergolide)**

## Drugs causing photosensitivity

Rash on the **forearms** and **face** is typical of a photosensitivity rash

**Causes of drug-induced photosensitivity:**

- Tetracyclines, Sulphonamides, Ciprofloxacin
- **Sulphonylurea**
- NSAIDs e.g. piroxicam
- **Thiazides**
- **Amiodarone**
- **ACEIs & ARBs**
- Psoralens

## Drugs causing ocular problems (Visual disturbance)

**Cataracts:** Steroids
**Corneal opacities:**
- **Amiodarone**
- Indomethacin

**Optic neuritis:**
- **Amiodarone**
- Ethambutol
- Metronidazole

**Retinopathy:** Chloroquine, quinine >> blindness
**Yellow- green tinge in vision: Digoxin**
**Blue tinge in vision: Sildenafil**

**Sildenafil** can cause both **blue discolouration** and **non-arteritic anterior ischaemic neuropathy.**
**Sildenafil** is a **PDE-5 inhibitor**, but at **high** dose it inhibits the activity of **PDE-6,** which is essential for the functioning of retinal rods cells. Inhibition of the enzyme leads to patients reporting blue tinged vision, particularly in low light conditions.

## Drug-induced impaired glucose tolerance IGT

**Drugs which are known to cause impaired glucose tolerance include:**
- **Steroids**
- **Thiazides**, **furosemide** (less common)
- **Tacrolimus**, **Cyclosporine**
- Interferon-**alpha**
- **Nicotinic acid (Vit. B3).**
- Atypical antipsychotics e.g. **Olanzapine**

Beta-blockers cause a slight impairment of glucose tolerance. They should also be used with caution in diabetics as they can interfere with the metabolic and autonomic responses to hypoglycaemia

## Drug causes of urticaria

**The following drugs commonly cause urticaria:**
- **Aspirin**
- NSAIDs
- Penicillins
- Opiates

Aspirin is a common cause of urticaria

## Drugs cause sensorineural deafness

- **Lasix IV** especially in bolus form, but oral Lasix is unlikely to cause a significant hearing loss.
- **Vancomycin IV.**
- **Erythromycin IV.**

## Drugs causing Gynecomastia

**Oestrogen and Oestrogen-like drugs:**

- Digoxin
- DES (Diethyl stilbosterol)
- OCP
- Cosmetics or food containing Oestrogen.

**Drugs which enhance Oestrogen formation:**

- Gonadotropins.
- Clomiphene

**Drugs which inhibit testosterone synthesis or action:**

- Spironolactone.
- Cimetidine.
- Ketoconazole.
- Alkylating agents: Cisplatin
- Metronidazole.

**Drugs whose mechanism of action is unknown:**

- Methyldopa.
- ACEI: (Captopril, Lisinopril).
- CCB (verapamil with long term use)
- Amiodarone
- Simvastatin
- TCA
- Heroin
- Marijuana
- INH
- Busulphan

## Drug-induced liver disease

Drug-induced liver disease is generally divided into hepatocellular, cholestatic or mixed. There is however considerable overlap, with some drugs causing a range of changes to the liver.

**The following drugs tend to cause a hepatocellular (Hepatitis) picture:**

- Alcohol
- Paracetamol
- **Halothane**
- Phenytoin
- Sodium valproate
- MAOIs
- Anti-tuberculosis: Rifampicin, Isoniazid, Pyrazinamide

- Nitrofurantoin
- **Statins**
- **Methyldopa**
- **Amiodarone**

**The following drugs tend to cause Mixed Cholestasis (+/- Hepatitis):**

- **Oral contraceptive pill**
- Antibiotics: **Flucloxacillin, Co-amoxiclav, Erythromycin, Azithromycin, Ciprofloxacin, Ofloxacin.**
- Anabolic steroids, testosterones
- **Phenothiazines**: Chlorpromazine, Prochlorperazine
- **Sulphonylurea**
- **Fibrates**
- Rare reported causes: Nifedipine, Captopril

Co-amoxiclav (Augmentin) is notorious for causing **drug-induced jaundice**, often with a **mixed hepatitis/cholestatic** picture. A 4 week **delay** in symptoms and signs is not unusual.

The patient must be warned that this could **reoccur** if he is given co-amoxiclav again.

Because of cholestatic jaundice, prescription of co-amoxiclav is not recommended for longer than 14 days.

## Liver cirrhosis:

- Methotrexate
- Methyldopa
- Amiodarone

## Haemodialysis in drug overdose

| Can be cleared with haemodialysis mnemonic: BLAST | Cannot be cleared with haemodialysis |
|---|---|
| 1) Barbiturate.<br>2) Lithium.<br>3) Alcohol (methanol, ethylene glycol).<br>4) Salicylates.<br>5) Theophylline (charcoal haemoperfusion is preferable). | 1) BDZ<br>2) TCA<br>3) Beta-blockers<br>4) Digoxin<br>5) Dextropropoxyphene (Co-proxamol) |

# Corticosteroids

Corticosteroids are amongst the most commonly prescribed therapies in clinical practice. They are used both systemically (oral or intravenous) or locally (skin creams, inhalers, eye drops, intra-articular).

They augment and in some cases replace the natural glucocorticoid and mineralocorticoid activity of endogenous steroids.

The relative glucocorticoid and mineralocorticoid activity of commonly used steroids is shown below:

| Minimal glucocorticoid activity, very high mineralocorticoid activity, | Glucocorticoid activity, high mineralocorticoid activity, | Predominant glucocorticoid activity, low mineralocorticoid activity | Very high glucocorticoid activity, minimal mineralocorticoid activity |
|---|---|---|---|
| **Fludrocortisone** | **Hydrocortisone** | **Prednisolone** | **Dexamethasone**<br>**Betamethasone** |

This is clinically relevant as there are some situations where it is important to combine high glucocorticoid (anti-inflammatory) activity with minimal mineralocorticoid (fluid-retention) effects. A good example is the use of **dexamethasone** for patients **with raised intracranial pressure** secondary to **brain tumours**.

## Side-effects:

The side-effects of corticosteroids are numerous and represent the single greatest limitation on their usage.

**Side-effects are more common with systemic and prolonged therapy.**

## Glucocorticoid side-effects:

- **Endocrine:** impaired glucose regulation, increased appetite/weight gain, hirsutism, and hyperlipidaemia.
- **Cushing's syndrome:** moon face, buffalo hump, striae.
- Musculoskeletal: **proximal myopathy**, **osteopenia** and **osteoporosis** rather than osteomalacia, **avascular necrosis** of the femoral head. (**Osteoporosis >>> which leads to Vertebral collapse**).
- **Immunosuppression:** increased susceptibility to severe infection, reactivation of tuberculosis.
- **Psychiatric:** insomnia, mania, depression, psychosis.

- **GIT:** peptic ulceration, acute pancreatitis.
- **Ophthalmic:** glaucoma, cataracts.
- **Suppression of growth in children.**
- **Intracranial hypertension.**

**Mineralocorticoid side-effects:**

- Fluid retention
- Hypertension

**Selected points on the use of corticosteroids:**

- **Patients on long-term steroids** should have their doses **doubled** during **intercurrent illness**.
- The BNF suggests **gradual withdrawal** of **systemic** corticosteroids if patients have: received **more than 40mg prednisolone daily** for **more** than **one week**, received more than 3 weeks treatment or recently received repeated courses.

Patients on long-term steroids should have their doses doubled during intercurrent illness.

**Proximal myopathy**, **easy bruising** and **thin skin** are clinical features that are **most suggestive of Cushing's syndrome**.
Otherwise, abdominal striae, buffalo hump, and acanthosis nigricans are all features of obesity.

**Corticosteroids** are recognised to **inhibit osteoblast activity** and **increase osteoblast apoptosis**. This is thought to be a more important component in bone loss with respect to **steroid induced osteoporosis** versus any effect on osteoclasts.
Patients taking **7.5 mg or more of prednisolone daily for 3 months or longer** should be offered **osteoprotection**.
The most appropriate therapy advocated by the National Osteoporosis Society for the **prevention of steroid-induced osteoporosis** would be **bisphosphonate** therapy such as Didronel or alendronate.
These are the **only class** of drug shown to offer osteoprotection with steroid therapy.

**EX**: 26-year-old male **body builder** + **azoospermia** + Lab: **low FSH** and **low LH** but with **normal testosterone**.
The most likely diagnosis is **steroid-induced hypogonadism**.
**Body builders** may be involved in the illicit use of **anabolic and androgenic steroids**. These results are consistent with ongoing use of androgens. The hypogonadism if persistent may be treated with human chorionic gonadotropin.

# Allopurinol

Allopurinol is used in the prevention of gout.

It works by inhibiting xanthine oxidase which is responsible for the oxidation of 6-mercaptopurine to 6-thiouric acid.

## Indications for allopurinol:

- Recurrent attacks - the British Society for Rheumatology recommend 'In uncomplicated gout uric acid lowering drug therapy should be started if a second attack, or further attacks occur within 1 year'.
- Tophi.
- Renal disease.
- Uric acid renal stones.
- Prophylaxis if on cytotoxics or diuretics.
- Patients with Lesch-Nyhan syndrome often take allopurinol for life.

Patients receiving CHOP for non-Hodgkin's lymphoma are at particular risk of tumour lysis syndrome and associated gout secondary to hyperuricaemia. Allopurinol is therefore normally co-prescribed to reduce this risk.

## Initiating allopurinol prophylaxis:

- Allopurinol **should not be started until 2 weeks after an acute attack has settled.**
- **Initial** dose of **100 mg OD**, with the dose titrated every few weeks to aim for a serum uric acid of < 300 µmol/l.
- **NSAID** or **colchicine** cover should be used when starting allopurinol.

## Interactions:

### Azathioprine (Imuran):

- Metabolised to active compound 6-mercaptopurine.
- Xanthine oxidase is responsible for the oxidation of 6-mercaptopurine to 6-thiouric acid.
- Allopurinol can therefore lead to high levels of 6-mercaptopurine.
- A much reduced dose (e.g. 25%) must therefore be used if the combination cannot be avoided.

### Cyclophosphamide:

- Allopurinol reduces renal clearance, therefore may cause marrow toxicity.

# Adrenaline

Adrenaline is a sympathomimetic amine with both alpha and beta adrenergic stimulating properties.

## Indications:

- Anaphylaxis
- Cardiac arrest

**Recommend Adult Life Support (ALS) adrenaline doses:**

- Anaphylaxis: **0.5ml 1:1,000 IM**
- Cardiac arrest: **1ml of 1:1000 IV** or **10ml 1:10,000 IV**

10ml of the 1:10,000 preparation contains 1mg of adrenaline.

**Management** of accidental injection: **Local infiltration of Phentolamine.**

Phentolamine, **a short acting alpha blocker**, may be used in this situation. It is normally used mainly to control blood pressure during surgical resection of Phaeochromocytoma.

Adrenaline induced ischaemia >>> treatment:**Local infiltration** with **Phentolamine**

# Antiarrhythmics: Vaughan Williams classification

It is still widely used although it should be noted that a number of common drugs are not included in the classification e.g. adenosine, atropine, digoxin and Mg.

AP = action potential

| Class | Examples | Mechanism of action | Notes |
|---|---|---|---|
| **Ia** | Quinidine<br>Procainamide<br>Disopyramide<br>+<br>Amiodarone | Block **sodium** channels<br>**Increases** AP duration | Quinidine toxicity causes **cinchonism** (headache, tinnitus, thrombocytopaenia)<br>Procainamide may cause drug-induced lupus |
| **Ib** | Lidocaine Phenytoin<br>Mexiletine<br>Tocainide | Block **sodium** channels<br>**Decreases** AP duration | |
| **Ic** | Flecainide<br>Propafenone<br>Encainide | Block **sodium** channels<br>**No** effect on AP duration | |
| **II** | Propranolol<br>Atenolol<br>Bisoprolol<br>Metoprolol | **Beta-**adrenoceptors antagonists | |
| **III** | Amiodarone<br>Sotalol<br>Ibutilide<br>Bretylium | Block **potassium** channels | |
| **IV** | Verapamil<br>Diltiazem | **Calcium** channel blockers | |
| **V** | Adenosine Digoxin<br>K+ ions Mg++ ions | **OTHERS** | |

# Calcium channel blockers (CCB)

CCBs are primarily used in the management of cardiovascular disease.

Voltage-gated calcium channels are present in myocardial cells, cells of the conduction system and those of the vascular smooth muscle.

The various types of calcium channel blockers have varying effects on these three areas and it is therefore important to differentiate their uses and actions.

**Mode of action**: ↓ Ca entry to smooth and cardiac muscle which in turn results in a ↓ force of contraction and slower heart rate.

## Indications:

- HTN
- Angina
- Arrhythmias (narrow complex tachycardia)
- Raynaud's

| Examples | Indications & notes | Side-effects and cautions |
|---|---|---|
| **Verapamil** | Angina, hypertension, arrhythmias.<br>Highly negatively inotropic.<br>**Should not be given with beta-blockers as may cause heart block.** | Heart failure, constipation, hypotension, bradycardia, flushing. |
| **Diltiazem** | Angina, hypertension.<br>Less negatively inotropic than verapamil but caution should still be exercised when patients have heart failure or are taking beta-blockers. | Hypotension, bradycardia, heart failure, ankle swelling. |
| **Nifedipine, Amlodipine, Felodipine (dihydropyridines)** | Hypertension, angina, Raynaud's.<br>Affects the **peripheral vascular smooth muscle** more than the myocardium and therefore do not result in worsening of heart failure. | Flushing, headache, ankle swelling |

## Dipyridamole

Dipyridamole is an antiplatelet mainly used in combination with aspirin after an ischaemic stroke or transient ischaemic attack.

### Mechanism of action:

- **Inhibits phosphodiesterase**, elevating platelet cAMP levels which in turn reduce intracellular calcium levels.
- Other actions include reducing cellular uptake of adenosine and **inhibition of thromboxane synthase**.

Dipyridamole inhibits phosphodiesterase

## Loop diuretics

**Furosemide (Lasix ®)** and **Bumetanide (Burinex ®)** are loop diuretics that act by **inhibiting the Na-K-Cl cotransporter** in the **thick ascending limb of the loop of Henle**, reducing the absorption of NaCl.

The name of **Lasix** is derived from **lasts six** (hours) referring to its duration of action.

### Indications:

- **Heart failure**: both acute (usually IV) and chronic (usually orally).
- **Resistant hypertension**, particularly in patients **with renal** impairment.

### Adverse effects:

- Hypotension
- Hyponatraemia
- Hypokalaemia
- Hypocalcaemia
- Hypochloraemic alkalosis (**Hyper** PH)
- **Hyper**glycaemia (less common than with thiazides)
- **Hyper**uricaemia Gout
- Ototoxicity
- Renal impairment (from dehydration + direct toxic effect)

## Finasteride

Finasteride is an inhibitor of 5 alpha-reductase, an enzyme which metabolises testosterone into dihydrotestosterone.

### Indications

- benign prostatic hyperplasia
- male-pattern baldness

### Adverse effects

- impotence
- decrease libido
- ejaculation disorders
- gynaecomastia and breast tenderness

Finasteride causes decreased levels of serum prostate-specific antigen

## Flecainide

Flecainide is a Vaughan Williams class 1c antiarrhythmic. It slows conduction of the action potential by acting as a potent **sodium channel blocker (specifically the Nav1.5 sodium channels)**. This may be reflected by widening of the QRS complex and prolongation of the PR interval.

The Cardiac Arrhythmia Suppression Trial (CAST, 1989) investigated the use of agents to treat asymptomatic or mildly symptomatic premature ventricular complexes (PVCs) post myocardial infarction.
The hypothesis was that this would reduce deaths from ventricular arrhythmias. Flecainide was actually shown to increase mortality post-myocardial infarction and is, therefore, contraindicated in this situation.

### Indications

- atrial fibrillation
- SVT associated with accessory pathway e.g. Wolf-Parkinson-White syndrome

### Contraindications

- post myocardial infarction
- structural heart disease: e.g. heart failure
- sinus node dysfunction; second-degree or greater AV block
- atrial flutter

### Adverse effects

- negatively inotropic
- bradycardia
- proarrhythmic
- oral paraesthesia
- visual disturbances

## Bendroflumethiazide

Bendroflumethiazide (bendrofluazide) is a thiazide diuretic which works by **inhibiting sodium absorption** at the **beginning (proximal part) of the distal convoluted tubule (DCT).**

**Potassium is lost** as a result of:

- **More sodium reaching the collecting ducts** causes the Na-K exchanger to release more K into the urine.
- **Another** cause is **activation of the renin-angiotensin-aldosterone system (RAAS)** secondary to hypovolaemia.

**Bendroflumethiazide >>> mechanism of hypokalaemia:**

1) Increased sodium reaching the collecting ducts.
2) Activation of the renin-angiotensin-aldosterone.

Bendroflumethiazide has a role in the treatment of mild heart failure although loop diuretics are better for reducing overload.

The main use of bendroflumethiazide currently is in the management of **hypertension** (as part of the effect is due to vasodilatation) but recent NICE guidelines now recommend other thiazide-like diuretics such as **indapamide** and **chlorthalidone**.

### Common adverse effects:

- Dehydration
- Postural hypotension
- Hyponatraemia
- Hypokalaemia
- **Hypercalcaemia**
- **Hyperuricaemia**
- **Hyperglycaemia** Impaired glucose tolerance
- Impotence

### Rare adverse effects:

- Agranulocytosis
- Thrombocytopaenia
- Photosensitivity rash
- Pancreatitis

## Spironolactone

Spironolactone is an aldosterone antagonist which acts act in **the distal convoluted tubule (DCT).**

### Indications:

- Ascites: patients with cirrhosis usually develop a secondary hyperaldosteronism. So that relatively large doses such as 100 or 200mg up to 400 mg daily are often used.

- Heart failure.
- Nephrotic syndrome.
- Conn's syndrome.

**Adverse effects:**

- Hyperkalaemia
- Gynaecomastia

**RALES:**

- NYHA III + IV, patients already taking ACE inhibitor.
- Low dose spironolactone reduces all-cause mortality.

**NB:** In the setting of AF, spironolactone may be used if the patient is thought to be in heart failure (which is fairly common with atrial fibrillation). In addition, spironolactone has been shown to **reduce the recurrence rate of atrial fibrillation following cardioversion** and so it is possible it would be started for this reason.

## Octreotide

**Overview:**

- Long-acting analogue of **somatostatin.**
- Somatostatin is released from D cells of pancreas and inhibits the release of growth hormone, glucagon and insulin.

**Uses:**

- **Acute treatment of variceal haemorrhage**
- **Acromegaly**
- **Carcinoid syndrome**
- Prevent complications **following pancreatic surgery**
- **VIPomas**
- **Refractory diarrhoea**

**Adverse effects:** Gallstones (secondary to biliary stasis).

## Proton pump inhibitors (PPI)

Proton pump inhibitors (PPI) are a group of drugs which profoundly reduce acid secretion in the stomach.

- They **irreversibly blocking** the hydrogen/potassium adenosine triphosphatase enzyme system (the **$H^+/K^+$ ATPase**) of the gastric **parietal cell.**
- PPI can reduce gastric acid secretion by up to **99%.** Acid production resumes following the normal renewal of gastric parietal cells.
- Examples include omeprazole and lansoprazole.

## Isotretinoin

Isotretinoin is an oral retinoid used in the treatment of **severe acne**.

It is highly effective in ttt of Acne Vulgaris, it decrease sebum production and sebaceous gland size.

Two-thirds of patients have a long term remission or cure following a course of oral Isotretinoin.

It is a synthetic 13-cis isomer of naturally occurring trans-retinoic acid.

### Adverse effects:

- **Highly Teratogenicity**: so females should ideally be using two forms of contraception (e.g. combined oral contraceptive pill and condoms), she should have **pre-ttt negative pregnancy test** and commit to effective contraception for **at least one month pre-ttt** and for **at least one month after** the cessation of treatment
- **Depression.**
- **Dry** skin, eyes and lips: the most common side-effect of Isotretinoin.
- **Nose bleeds** (caused by dryness of the nasal mucosa).
- Hair thinning.
- Photosensitivity.
- Raised **triglycerides**.
- **Benign intracranial hypertension & papilledema**: Isotretinoin treatment should not be combined with tetracyclines for this reason.
- Isotretinoin has been known to **reduce** ↓ plasma concentration of Carbamazepine.

## Heparin

There are two main types of heparin - unfractionated, 'standard' heparin or low molecular weight heparin (LMWH). Heparins generally act by activating antithrombin III. Unfractionated heparin forms a complex which inhibits thrombin, factors Xa, IXa, XIa and XIIa. LMWH however only increases the action of antithrombin III on factor Xa

### Adverse effects of heparins include:

- bleeding
- **thrombocytopenia** - see below
- **osteoporosis** and an increased risk of fractures
- **hyperkalaemia** - this is thought to be caused by inhibition of aldosterone secretion

The table below shows the differences between standard heparin and LMWH:

| | Standard heparin | Low molecular weight heparin (LMWH) |
|---|---|---|
| **Administration** | Intravenous | Subcutaneous |
| **Duration of action** | Short | Long |
| **Mechanism of action** | **Activates antithrombin III. Forms a complex that inhibits thrombin, factors Xa, IXa, Xia and XIIa** | **Activates antithrombin III. Forms a complex that inhibits factor Xa** |
| **Side-effects** | Bleeding<br>Heparin-induced thrombocytopaenia (HIT)<br>Osteoporosis | Bleeding<br><br>Lower risk of HIT and osteoporosis with LMWH |
| **Monitoring** | Activated partial thromboplastin time (APTT) | Anti-Factor Xa (although routine monitoring is not required) |
| **Notes** | Useful in situations where there is a high risk of bleeding as anticoagulation can be terminated rapidly. Also useful in renal failure | Now standard in the management of venous thromboembolism treatment and prophylaxis and acute coronary syndromes |

### Heparin-induced thrombocytopaenia (HIT)

- immune mediated - antibodies form against complexes of platelet factor 4 (PF4) and heparin
- these antibodies bind to the PF4-heparin complexes on the platelet surface and induce platelet activation by cross-linking FcγIIA receptors
- usually does not develop until after 5-10 days of treatment
- despite being associated with low platelets HIT is actually a prothrombotic condition
- features include a greater than 50% reduction in platelets, thrombosis and skin allergy
- address need for ongoing anticoagulation:
  - direct thrombin inhibitor e.g. argatroban
  - danaparoid

Heparin overdose may be reversed by protamine sulphate, although this only partially reverses the effect of LMWH.

## Interferon (IFN)

Interferons (IFN) are cytokines released by the body in response to viral infections and neoplasia.

They are classified according to cellular origin and the type of receptor they bind to.

IFN-alpha and IFN-beta bind to the same type of receptor **type 1 receptors** whilst IFN-gamma binds **only to type 2 receptors.**

**IFN-alpha:**

- Produced by **leucocytes**.
- Antiviral action.
- Useful in hepatitis **B** & **C**, **Kaposi's** sarcoma, **metastatic renal cell cancer** and **hairy cell leukaemia**.
- Adverse effects include **flu-like symptoms** and **depression.**

**IFN-beta:**

- Produced by **fibroblasts**.
- Antiviral action.
- Reduces the frequency of exacerbations in patients with relapsing-remitting **MS**.

**IFN-gamma:**

- Produced by **T** lymphocytes & **NK** cells.
- **Weaker** antiviral action, more of a role in immunomodulation particularly macrophage activation.

May be useful in **chronic granulomatous disease** and **osteopetrosis**

## Sildenafil

Sildenafil is a **phosphodiesterase type V (5) inhibitor** used in the treatment of impotence.

**Side-effects:**

- Visual disturbances e.g. **blue discolouration**, **non-arteritic anterior ischaemic optic neuropathy.**
- Nasal congestion.
- Flushing.
- Headache.
- Gastrointestinal side-effects.

## Contraindications:

- Hypotension.
- Patients taking **Nitrates** and related drugs such as **Nicorandil.**
- Recent **stroke** or **myocardial infarction**.
- Non-arteritic anterior ischaemic optic neuropathy.
- Other patients in which PPD5 inhibitors should be used with caution are those with risk of **priapism**, such as **sickle cell** or **multiple myeloma**.

The BNF recommends **avoiding alpha-blockers (e.g. Doxazosin) for 4 hours after** sildenafil.

**Visual changes secondary to drugs:**

- **Blue** vision: Viagra (**'the blue pill'**)
- Yellow-green vision: Digoxin

# Immunoglobulins: Therapeutics

## Basics:

- It is formed from large pool of donors e.g. 5000 persons.
- IgG molecules with a subclass distribution similar to that of normal blood.
- Half-life of 3 weeks.

## Uses:

- Primary and secondary **immunodeficiency**.
- **ITP** (idiopathic thrombocytopenic purpura) **(NOT TTP).**
- **Myasthenia gravis**
- **GBS**
- **CIDP** (chronic inflammatory demyelinating polyradiculopathy).
- **Kawasaki disease**
- **TEN**
- **Dermatomyositis**.
- Pneumonitis induced by CMV following transplantation
- ↓ Serum IgG levels following haematopoietic stem cell transplant for malignancy.

# Statins

Statins inhibit the action of **HMG-CoA reductase**, the rate-limiting enzyme in **hepatic cholesterol synthesis**.

Most circulating cholesterol is manufactured **internally**, in amounts of about 1000 mg/day, via carbohydrate metabolism through the HMG-CoA reductase pathway.

## Adverse effects:

- **Myopathy**: (occurs in up to **5%** of those treated with statins)
  - Includes myalgia, myositis, **rhabdomyolysis** and **asymptomatic raised creatine kinase.**
  - ↑ CPK levels more than ten times normal.
  - **Risks factors** for myopathy include **advanced age**, **female** sex, **low BMI** and presence of multisystem disease such as **DM.**
  - Myopathy is more common in **lipophilic** statins (simvastatin, atorvastatin) than relatively hydrophilic statins (rosuvastatin, pravastatin, fluvastatin).
  - Myalgia can gradually improve with time, dose reduction, or changing to an alternative statin. Pravastatin and rosuvastatin are metabolised via different pathways when compared to simvastatin and atorvastatin. Pravastatin may be suitable for primary prevention, but in this high-risk secondary prevention patient, a stronger agent is required. **Rosuvastatin can be effective at even low doses (5-10 mg).**
  - It may be exacerbated by the co-prescription of other drugs such as **CCBs (deltiazem and verapamil), macrolide** antibiotics, fibrates, and **amiodarone** and **grapefruit** juice.
- **Liver impairment**: the 2008 NICE guidelines recommend checking LFTs at **baseline**, **3 months** and **12 months**.

> Treatment with Statins should be **discontinued if** serum transaminase concentrations **rise to and persist at 3 times** the upper limit of the reference range.

- There is some evidence that statins may **increase the risk of intracerebral haemorrhage** in patients who've previously had a **stroke**. This effect is not seen in primary prevention. For this reason the Royal College of Physicians recommend **avoiding statins in patients with a history of intracerebral haemorrhage.**

Cytochrome P450 **inhibitors** >>> ↑ **CPK** >>> **Myopathy**

**EX**: A 67-year-old female is prescribed simvastatin for hyperlipidaemia. Which one of the following juice is most likely to interact with her medication? >> **Grapefruit juice** is a potent **inhibitor** of the cytochrome P450 enzyme CYP3A4.

Statins should be **discontinued** in **women 3 months before conception** due to the risk of **congenital defects**.

**Ezetimibe monotherapy** produces reductions in TC and LDL-C of around **20%** and since tolerability issues are likely to occur with another statin.

### Who should receive a statin?

- **All people with established cardiovascular disease** (**Stroke**, **TIA**, **IHD**, and **PVD**).
- NICE recommend **anyone with a 10-year cardiovascular risk ≥ 20%.**
- The management of blood lipids in type 2 diabetes mellitus (T2DM) has changed slightly:
  - **Previously, all patients with T2DM > 40-years-old** were prescribed statins.
  - **Now,** Patients > 40-years-old who have no obvious cardiovascular risk (e.g. Non-smoker, not obese, normotensive etc.) and have a cardiovascular risk < 20%/10 years **do not need** to be given a statin.

Statins should be taken **at night (Last thing in the evening)** as this is when the majority of cholesterol synthesis takes place. This is especially true for simvastatin which has a shorter half-life than other statins.

Current NICE guidelines do **not** recommend a **target** cholesterol in **primary** prevention. (**NO Target level of lipid profile in primary prevention**).

Current guidelines for lipid lowering (for secondary prevention):

| | Total cholesterol | LDL cholesterol |
|---|---|---|
| Joint British Societies | **< 4.0** | **< 2.0** |
| National Service Framework for CHD | < 5.0 | < 3.0 |
| SIGN 2007 | < 5.0 | < 3.0 |

# Hyperlipidaemia: mechanism of action and adverse effects

The following table compares the side-effects of drugs used in hyperlipidaemia:

| Drugs | Mechanism of action | Adverse effects |
|---|---|---|
| Statins | **HMG CoA reductase inhibitors**. | Myositis, deranged LFTs |
| Ezetimibe | It localises at the brush border of the small intestine,<br>So it **decreases cholesterol absorption in the small intestine.** | Headache |
| Nicotinic acid | Decreases hepatic VLDL secretion.<br>**Inhibit lipolysis** of adipocytes. | Flushing, pruritis, IGT, myositis |
| Fibrates | **Agonist** of **PPAR-alpha** therefore **↑lipoprotein lipase expression** so:<br>↓ **LDL** by 5-25%, ↑**HDL** by 15-30% and ↓**TG** (via ↓VLDL) by 20-60%. | Myositis, pruritus, cholestasis, **GB stones** |
| Cholestyramine | Decreases bile acid reabsorption in the small intestine (**Bile acid sequestration**), up regulating the amount of cholesterol that is converted to bile acid. | GI side-effects |
| **OMACOR** (omega-3-acid ethyl esters) Icosalip or exceedolip | **Increases peroxisomal beta-oxidation of fatty acids in the liver.**<br>It reduces triglycerides by different, independent effects in the liver.<br>It reduces production of TG in the liver, as EPA and DHA are poor substrates for the enzymes responsible for triglyceride synthesis.<br>EPA and DHA also inhibit esterification of other fatty acids. | |

NB: **Fibrates** and **nicotinic acid** have been associated with myositis, especially when combined with a **statin**. So take warns about the concomitant prescription of fibrates with statins in relation to muscle toxicity.

## Nicotinic acid

It is used in the treatment of patients with hyperlipidaemia, although its use is limited by side-effects.

As well as **lowering cholesterol and triglyceride** concentrations it also **raises HDL levels**.

Nicotinic acid >>> ↓ TC, ↓ TG, ↑ **HDL.**

### Adverse effects:

- **Flushing**
- **Myositis**
- **Impaired glucose tolerance**

## Cyclosporine

Cyclosporine is an immunosuppressant was introduced in 1983 which decreases clonal proliferation of T cells by **reducing IL-2 release**.

It acts by binding to cyclophilin forming a complex which **inhibits calcineurin**, a phosphotase that activates various transcription factors in T cells.

**Action of cyclosporine:**

- Binds to cyclophilin forming a complex which **inhibits calcineurin**, a phosphotase that activates various transcription factors in T cells.
- Decreases clonal proliferation of T cells by **reducing IL-2 release.**

Cyclosporine + Tacrolimus >>>: **inhibit calcineurin** thus **decreasing IL-2.**

**Adverse effects of cyclosporine** (note how **everything is increased** - fluid, BP, $K^+$, hair, gums, glucose):

- **Nephrotoxicity:** (the most frequent)
- **Hepatotoxicity**
- Fluid retention
- **Hyper**tension
- **Hyper**kalaemia
- **Hyper**trichosis
- **Hyper**glycaemia (Impaired glucose tolerance)
- **Hyper**lipidaemia
- **Hyper**uricaemia (gout)

- Pancreatitis.
- Increased susceptibility to severe infection
- Gingival **hyper**plasia
- Coarse tremor
- Anaemia & Thrombocytopenia

Cyclosporine SE: everything is increased - fluid, BP, $K^+$, hair, gums, glucose

**NB: In post renal transplant**, the 2 most common causes of declining renal function are **graft rejection** and **cyclosporine toxicity.**

Interestingly for an immunosuppressant, cyclosporine is noted by the BNF to be 'virtually non-myelotoxic'.

### Indications:

- Following organ transplantation
- Rheumatoid arthritis
- Ulcerative colitis
- Pure red cell aplasia
- Psoriasis (has a direct effect on keratinocytes as well as modulating T cell function)
- Severe eczema in cases where conventional therapy has failed.

## Tacrolimus (Prograf ®)

Tacrolimus is a macrolide used as an immunosuppressant to prevent transplant rejection. It has a very similar action to cyclosporine.

The action of Tacrolimus differs in that it binds to a protein called **FKBP** rather than cyclophilin.

Tacrolimus is **more potent than cyclosporine** and hence the incidence of organ rejection is less. However, nephrotoxicity and impaired glucose tolerance is more common.

**Mycophenolate mofetil (MMF)** inhibits inosine monophosphate dehydrogenase.

**Methotrexate** is an antimetabolite which inhibits dihydrofolate reductase.

**Azathioprine** a purine analogue that inhibits purine synthesis.

# Monoclonal antibodies

- Monoclonal antibodies have an increasing role in medicine. They are manufactured by a technique called **somatic cell hybridization**.
- This involves the fusion of myeloma cells with spleen cells from a mouse that has been immunized with the desired antigen.
- The resulting fused cells are termed a hybridoma and act as a 'factory' for producing monoclonal antibodies.
- **The main limitation to this is that mouse antibodies are immunogenic leading to the formation of human anti-mouse antibodies.**
- **This problem is overcome by a process known as humanizing.**
- **One method involves combining the variable region from the mouse body with the constant region from a human antibody.**

## Clinical examples of monoclonal antibodies:

- **infliximab (anti-TNF):** used in rheumatoid arthritis and Crohn's
- **rituximab** (anti-CD20): used in non-Hodgkin's lymphoma and rheumatoid arthritis
- **cetuximab** (epidermal growth factor receptor antagonist): used in metastatic colorectal cancer and head and neck cancer
- **trastuzumab** (HER2/neu receptor antagonist): used in metastatic breast cancer
- **alemtuzumab** (anti-CD52): used in chronic lymphocytic leukaemia
- **abciximab** (glycoprotein IIb/IIIa receptor antagonist): prevention of ischaemic events in patients undergoing percutaneous coronary interventions
- **OKT3** (anti-CD3): used to prevent organ rejection

## Monoclonal antibodies are also used for:

- medical imaging when combined with a radioisotope
- identification of cell surface markers in biopsied tissue
- diagnosis of viral infections

# Lithium

Lithium is mood stabilising drug used most commonly prophylactically in **bipolar** disorder but also as an adjunct in refractory depression.

It has a **very narrow therapeutic range (0.5-1.0 mmol/L)** and a long plasma half-life being excreted primarily by the kidneys.

## Mechanism of action - not fully understood, two theories:

- Interferes with inositol triphosphate formation
- Interferes with cAMP formation

## Adverse effects:

- **Goiter In 40 %,** may lead to **hypothyroidism in 20 %**
- **Polyuria** (secondary to **nephrogenic diabetes insipidus**)
- Anorexia/Nausea/Vomiting, **diarrhoea**
- **Fine tremor**
- **ECG**: T wave flattening/inversion
- **Weight gain**
- **Hypercalcaemia (Raise ↑ serum Ca)**
- **Hypermagnesaemia (Raise ↑ serum Mg)**

Lithium: **fine tremor** in chronic treatment, **coarse tremor** in acute toxicity.

**Lithium >>> Hypothyroidism >>> Hyperprolactinaemia >>> Infertility**

"The common clinical side effects of the lithium are **goitre** in up to **40%** and hypothyroidism in about **20%**. Lithium increases thyroid autoimmunity if present before therapy. Treatment with **levothyroxine** is effective and **lithium therapy should not be stopped."**

### Monitoring of patients on lithium therapy:

- Inadequate monitoring of patients taking lithium is common - NICE and the National Patient Safety Agency (NPSA) have issued guidance to try and address this. As a result it is often an exam hot topic.
- **Lithium blood level** should 'normally' **be checked every 3 months**. Levels should be **taken 12 hours post-dose.**
- **Thyroid** and **renal** function should be checked **every 6 months**.
- GGT is the most sensitive measure of the effects of lithium on the liver.
- Patients should be issued with an information booklet, alert card and record book.

# Lithium toxicity

Lithium toxicity generally occurs following concentrations **> 1.5** mmol/L.

**Toxicity may be precipitated by:**

- Dehydration
- Diuretics (especially **Thiazide**): it may result in paradoxical salt & water retention and possible Lithium intoxication.
- Renal failure
- **NSAIDs**
- **ACEI** & **ARBs**.
- **CCB (Verapamil & Diltiazem)**
- **Metronidazole** is the only antibiotic listed in the BNF that may interact with lithium.

**BNF** advises that **neurotoxicity** may be ↑ when lithium is given with **diltiazem** or **verapamil** but there is no significant interaction with **amlodipine.**
**Atenolol**, in contrast, is a relatively **safer** option for the treatment of hypertension in association with long term lithium use.
**Alpha-blockers** are not listed as interacting with lithium **but** they would not be first-line treatment for hypertension.

## Features of toxicity:

- **Coarse tremor** (a fine tremor is seen in therapeutic levels)
- Anorexia, nausea, vomiting, diarrhea
- **Ataxia**, **Nystagmus**, **Dysarthria**, **hyperreflexia**
- Acute confusion, Seizure, Coma
- **Cardiovascular** adverse effects are more likely to occur in the presence of underlying cardiac disease: **hypotension**, **bradycardia** and **heart block.**

## Management:

- Mild-moderate toxicity (levels less than 2mmol/L) may respond to **volume resuscitation with normal saline.**
- In **severe** toxicity (as in **high** lithium level and **reduced GCS**) >>> **Haemodialysis** may be needed.
- **Sodium bicarbonate** is sometimes used but there is **limited** evidence to support this. By increasing **the alkalinity of the urine** it promotes lithium excretion.

In acute or chronic toxicity, a **lithium level of greater than 4 mmol/L** or features of **central nervous system** toxicity or **cardiac instability** are indications for **haemodialysis**.

Activated charcoal does **not** bind lithium effectively and is therefore ineffective except where co-ingestion of other poisons is suspected.

10% of patients who survive from severe lithium toxicity will be left with a neurological deficit.

**EX**: Pt with bipolar disorder on lithium then develop polyuria and weight gain >>? **D.I** >>> **admission for water deprivation test and ADH administration**.

## Monoamine oxidase inhibitors (MAOIs)

### Overview:

- Serotonin and noradrenaline are metabolised by monoamine oxidase (MAO) in the presynaptic cell.

**Non-selective monoamine oxidase inhibitors (MAOI):**

- EX. Tranylcypromine, Phenelzine.
- Used in the treatment of atypical depression (e.g. hyperphagia) and other psychiatric disorder.
- Not used frequently due to side-effects.

**Adverse effects of non-selective monoamine oxidase inhibitors:**

- Hypertensive reactions with **tyramine containing foods** e.g.
  - **Cheese**
  - **Pickled herring**
  - **Bovril**
  - **Oxo**
  - **Marmite**
  - **Broad beans**
- Anticholinergic effects.

# Benzodiazepines (BDZs)

Benzodiazepines **enhance** the effect of the inhibitory neurotransmitter gamma-aminobutyric acid (**GABA**) by increasing the **frequency** of **chloride channels**.

BDZs **enhance the effect of GABA, the main inhibitory neurotransmitter**

**They therefore are used for a variety of purposes:**

- Sedation
- Hypnotic
- Anxiolytic
- Anticonvulsant
- Muscle relaxant

Patients commonly develop a **tolerance** and **dependence** to benzodiazepines and care should therefore be exercised on prescribing these drugs.

The Committee on Safety of Medicines advises that benzodiazepines are only prescribed for a short period of time (2-4 weeks).

The BNF gives advice on how to withdraw a benzodiazepine. The dose should be withdrawn in steps of about 1/8 (range 1/10 to 1/4) of the daily dose every fortnight. A suggested protocol for patients experiencing difficulty is given:

- Switch patients to the equivalent dose of diazepam.
- Reduce dose of diazepam every 2-3 weeks in steps of 2 or 2.5 mg.
- Time needed for withdrawal can vary from **4 weeks** to **a year or more**.

If patients withdraw too quickly from benzodiazepines they may experience **benzodiazepine withdrawal syndrome**, a condition **very similar to alcohol withdrawal syndrome.** This may occur up to 3 weeks after stopping a long-acting drug. Features include:

- Insomnia
- Irritability
- Anxiety
- Tremor
- **Loss of appetite**
- **Tinnitus**
- **Perspiration**
- **Perceptual disturbances**
- Seizures

BDZs antidote is >>> **Flumazenil**

**NB**: **Flumazenil** should **not** be given in **an unknown overdose** as it can often precipitate **seizures** especially in a **mixed** overdose with **tricyclics** (TCA) and benzodiazepines.

## Antihistamines

Antihistamines ($H_1$ inhibitors) are of value in the treatment of allergic rhinitis and urticaria.

Example of sedating antihistamines: Chlorpheniramine

As well as being sedating these antihistamines have some Antimuscarinic properties (e.g. urinary retention, dry mouth).

**Examples of non-sedating antihistamines:**

- **Loratidine**
- Cetirizine

Of the non-sedating antihistamines there is some evidence that cetirizine may cause more drowsiness than other drugs in the class.

## Combined oral contraceptive pill: contraindications

The decision of whether to start a women on the combined oral contraceptive pill is now guided by the UK Medical Eligibility Criteria (**UKMEC**).

**This scale categorises the potential cautions and contraindications according to a four point scale, as detailed below:**

- **UKMEC 1**: a condition for which there is no restriction for the use of the contraceptive method
- **UKMEC 2**: advantages generally outweigh the disadvantages
- **UKMEC 3**: disadvantages generally outweigh the advantages
- **UKMEC 4**: represents an unacceptable health risk

**Examples of UKMEC 3 conditions include: (= Relative contraindications):**

- More than 35 years old and smoking less than 15 cigarettes/day
- BMI > 35 kg/m2
- Migraine without aura and more than 35 years old
- Family history of thromboembolic disease in 1st degree relatives < 45yrs
- Controlled hypertension
- Immobility e.g. wheel chair use
- Breast feeding 6 weeks - 6 months postpartum

**Examples of UKMEC 4 conditions include: (= Absolute contraindications):**

- More than 35 years old and smoking more than 15 cigarettes/day
- Migraine with aura
- History of thromboembolic disease or thrombogenic mutation
- History of stroke or ischaemic heart disease
- Breast feeding < 6 weeks post-partum
- Uncontrolled hypertension
- Breast cancer
- Major surgery with prolonged immobilisation

## Advice on taking the pill, including

- if the COC is started within the first 5 days of the cycle then there is no need for additional contraception. If it is started at any other point in the cycle then alternative contraception should be used (e.g. condoms) for the first 7 days
- should be taken at the same time every day
- the COCP is conventionally taken for 21 days then stopped for 7 days - similar uterine bleeding to menstruation. However, there was a major change following **the 2019 guidelines**. 'Tailored' regimes should now be discussed with women. This is because there is no medical benefit from having a withdrawal bleed. Options include never having a pill-free interval or 'tricycling' - taking three 21 day packs back-to-back before having a 4 or 7 day break
- advice that intercourse during the pill-free period is only safe if the next pack is started on time

DM diagnosed > 20 y ago is classified as UKMEC 3 or 4 depending on severity.

# Progestogen only pill: advantages/disadvantages

## Advantages:

- Highly effective (failure rate = 1 per 100 woman years)
- Doesn't interfere with sex
- Contraceptive effects reversible upon stopping
- Can be used whilst breast-feeding
- Can be used in situations where the combined oral contraceptive pill is contraindicated e.g. in smokers > 35 years of age and women with a history of venous thromboembolic disease

### Disadvantages:

- **Irregular periods**: some users may not have periods whilst others may have irregular or light periods. This is **the most common adverse effect**
- Doesn't protect against sexually transmitted infections.
- Increased incidence of functional ovarian cysts.
- Common side-effects include breast tenderness, weight gain, acne and headaches. It may be associated with a **reduced libido**. These symptoms generally subside after the first few months.

The primary action of the **combined oral contraceptive pill** is **inhibition of ovulation**, although there are also alterations to the cervical mucus and endometrium which may contribute to effectiveness.
In contrast the **progesterone only pill** does not necessarily affect ovulation and its primary mode of action is **on cervical mucus (thicken cervical mucus) and prevent proliferation of the endometrium and implantation**.

## Hormone replacement therapy (HRT)

HRT involves the use of a **small dose of oestrogen** (combined with a **progestogen in women with a uterus**) to help alleviate menopausal symptoms.
The indications for HRT have changed significantly over the past ten years as the long-term risks became apparent, primarily as a result of the Women's Health Initiative (WHI) study.

### Indications:

- **Vasomotor symptoms** such as flushing, insomnia and headaches.
- **Premature menopause**: should be continued **until the age of 50 years.**
- **Osteoporosis**: but should only be used as **second**-line treatment.

The main indication of HRT is >>> the control of **vasomotor symptoms**.

The other indications such as reversal of vaginal atrophy and prevention of osteoporosis should be treated with other agents as first-line therapies.
Other benefits include a **reduced incidence of colorectal cancer**.

### Side-effects:

- Nausea.
- Breast tenderness.
- Fluid retention and weight gain.

### Potential complications:

- Increased risk of **breast cancer**: increased by the addition of a progestogen.

- Increased risk of **endometrial cancer**: ***reduced*** by the addition of a ***progestogen*** but not eliminated completely. The BNF states that the additional risk is eliminated if a progestogen is given continuously.
- Increased risk of **venous thromboembolism**: increased by the addition of a progestogen.
- Increased risk of **stroke**
- Increased risk of **IHD** if taken more than 10 years after menopause. (it frequently produces a **rise** in **triglyceride** concentrations).

**So, Combined OCP:**
- ↑ Risk of Breast cancer+ DVT+ Stroke+ IHD.
- ↓ Risk of Endometrial cancer.

**Breast cancer:**
- In the Women's Health Initiative (WHI) study there was a relative risk of 1.26 at 5 years of developing breast cancer.
- The increased risk relates to duration of use
- Breast cancer incidence is higher in women using combined preparations compared to oestrogen-only preparations.
- The risk of breast cancer begins to decline when HRT is stopped and by 5 years it reaches the same level as in women who have never taken HRT.

## Prescribing in pregnant patients

Very few drugs are known to be completely safe in pregnancy.
The list below largely comprises of those known to be harmful. Some countries have developed a grading system - see the link.

### Antibiotics:
- Tetracyclines
- Aminoglycosides
- Sulphonamides and trimethoprim
- Quinolones: the BNF advises to avoid due to arthropathy in some animal studies

### Other drugs:
- ACEI & ARBs
- Statins
- Warfarin
- Sulfonylureas
- Retinoids (including topical)
- Cytotoxic agents

The majority of antiepileptics including valproate, carbamazepine and phenytoin are known to be potentially harmful. The decision to stop such treatments however is difficult as uncontrolled epilepsy is also a risk.

## Breast feeding: contraindications

The major breastfeeding contraindications tested in exams relate to drugs (see below). Other contraindications of note include:

- Galactosaemia.
- Viral infections - this is controversial with respect to HIV in the developing world. This is because there is such an increased infant mortality and morbidity associated with bottle feeding that some doctors think the benefits outweigh the risk of HIV transmission.

**The following drugs can be given to mothers who are breast feeding:**

- Antibiotics: **Penicillins, Cephalosporins, Trimethoprim.**
- Hypertension: **Methyldopa, Hydralazine, Beta-blockers.**
- Digoxin.
- Anticoagulants: heparin, warfarin.
- Endocrine: glucocorticoids (avoid high doses), levothyroxine
- Epilepsy: sodium valproate, carbamazepine.
- Asthma: salbutamol, theophyllines.
- Psychiatric drugs: tricyclic antidepressants, antipsychotics (EXCEPT clozapine should be avoided).

**The following drugs should be avoided in breast feeding:**

- Antibiotics: Tetracycline, Sulphonamides, Chloramphenicol, Quinolones
- Psychiatric drugs: lithium, benzodiazepines, **clozapine**.
- **Amiodarone**
- **Aspirin**
- Carbimazole
- **Sulphonylureas**
- Cytotoxic drugs

Breast feeding is acceptable with nearly all anti-epileptic drugs taken in normal doses, with the possible exception of barbiturates.

EX: female with breast feeding and UTI >>> ttt: **Trimethoprim**

# Smoking Cessation Therapy

NICE released guidance on the management of smoking cessation. General points include:

- Patients should be offered nicotine replacement therapy **(NRT), varenicline** or **bupropion** - NICE state that clinicians should not favour one medication over another.
- NRT, varenicline or bupropion should normally be prescribed as part of a commitment to stop smoking **on or before a particular date** (target stop date).
- Prescription of NRT, varenicline or bupropion should be sufficient to last only until 2 weeks after the target stop date. Normally, this will be after 2 weeks of NRT therapy, and 3-4 weeks for varenicline and bupropion, to allow for the different methods of administration and mode of action. Further prescriptions should be given only to people who have demonstrated that their quit attempt is continuing.
- If unsuccessful using NRT, varenicline or bupropion, **do not offer a repeat prescription within 6 months unless** special circumstances have intervened.
- Do not offer NRT, varenicline or bupropion in any combination.
- Studies have shown success in smoking cessation in **20-30%** of patients involved in **Bupropion** studies at **1 year. (Bupropion has a greatest chance of quitting).**

## Nicotine Replacement Therapy (NRT):

- Adverse effects include nausea & vomiting, headaches and flu-like symptoms.
- NICE recommend offering a combination of nicotine patches and another form of NRT (such as gum, inhalator, lozenge or nasal spray) to people who show a high level of dependence on nicotine or who have found single forms of NRT inadequate in the past.

## Varenicline (Champix ®):

- A **Nicotinic receptor partial agonist.**
- Should be started **1 week before** the patient's target date to stop.
- The recommended course of treatment is **12 weeks** (but patients should be monitored regularly and treatment only continued if not smoking).
- Has been shown in studies to be **more effective than bupropion**.

- **Nausea** is the most common adverse effect. Other common problems include headache, insomnia, abnormal dreams.
- Varenicline should be used with caution in patients with **a past history of depression** or **deliberate self-harm**. There are ongoing studies looking at the risk of **suicidal** behaviour in patients taking varenicline.
- Contraindicated in pregnancy and breast feeding.

## Bupropion (Zyban ®):

- A **Norepinephrine and dopamine reuptake inhibitor**, and **Nicotinic antagonist**.
- Should be started **1 to 2 weeks before** the patient's target date to stop.
- Small risk of **seizures** (1 in 1,000)
- **Contraindicated in epilepsy**.
- Having an **eating disorder** is a **relative** contraindication.
- Contraindicated in pregnancy and breast feeding.

## Pregnant women:

NICE recommended in 2010 that all pregnant women should be tested for smoking using **carbon monoxide CO detectors**, partly because *'some women find it difficult to say that they smoke because the pressure not to smoke during pregnancy is so intense.'*

All women who smoke, or have stopped smoking within the last 2 weeks, or those with a CO reading of 7 ppm or above should be referred to NHS Stop Smoking Services.

## Interventions:

- The first-line interventions in pregnancy should be **cognitive behaviour** therapy, motivational interviewing or structured self-help and support from NHS Stop Smoking Services.
- The evidence for the use of **NRT** in pregnancy is mixed but it is often used if the above measures failure. There is no evidence that it affects the child's birth weight. Pregnant women should remove the patches before going to bed.
- As mentioned above, varenicline and bupropion are contraindicated in pregnancy and breast feeding.

# Aspirin

- Aspirin works by blocking the action of both **cyclooxygenase-1 and 2**.
- Cyclooxygenase is responsible for prostaglandin, prostacyclin and thromboxane synthesis.
- The blocking of **thromboxane A2** formation in platelets reduces the ability of platelets to aggregate which has led to the widespread use of low-dose aspirin in cardiovascular disease.
- Until recent guidelines changed all patients with established cardiovascular disease took aspirin if there was no contraindication. Following the 2010 technology appraisal of clopidogrel this is no longer the case*.
- Two recent trials (the Aspirin for Asymptomatic Atherosclerosis and the Antithrombotic Trialists Collaboration) have cast doubt on the use of aspirin in primary prevention of cardiovascular disease.
- Guidelines have not yet changed to reflect this. However the Medicines and Healthcare products Regulatory Agency (MHRA) issued a drug safety update in January 2010 reminding prescribers that aspirin is not licensed for primary prevention.

**What should receive aspirin according to the current guidelines?**

- All people with established cardiovascular disease (Stroke, TIA, IHD, PVD).
- All people aged ≥ 50 years with a 10- year cardiovascular risk ≥ 20%.
- All people with DM type I or II who are ≥ 50 years old or who have DM ≥ 10 years, taking ttt for HTN or evidence of target organ damage.
- All people with target organ damage from HTN.

**Potentiates:**

- Oral hypoglycaemics
- Warfarin
- Steroids

***NICE** now recommend clopidogrel first-line following an ischaemic stroke and for peripheral arterial disease. For TIAs the situation is more complex. Recent Royal College of Physician (RCP) guidelines support the use of clopidogrel in TIAs. However the older NICE guidelines still recommend aspirin + dipyridamole - a position the RCP state is 'illogical'.

**Aspirin** can be **continued normally** if patient is going for **dental** procedure

# Alcohol withdrawal

## Mechanism:

- Chronic alcohol consumption enhances GABA mediated inhibition in the CNS (similar to BDZ) and inhibits NMDA-type glutamate receptors.
- Alcohol withdrawal is thought to be led to the opposite (↓ inhibitory GABA and ↑NMDA glutamate transmission).

## Features:

- **Symptoms** start at **6-12 hours alcohol-free period.**
- Peak incidence of **seizures** at **36 hours.**
- Peak incidence of **delirium tremens** is at **72 hours.**

Approximately 20% of patients admitted to hospital for illnesses unrelated to alcohol are drinking at potentially hazardous levels, and it's therefore important to ask all patients about their alcohol use.

An abrupt reduction in alcohol intake in a person who has been drinking excessively for a prolonged period of time, for example as occurs on admission to hospital, may results in the development of alcohol withdrawal.

Symptoms typically present about 10 hours after a significant fall in blood alcohol levels.

The peak is on day 2, and by day 5 the symptoms are significantly better.

**Minor withdrawal symptoms appear 6-12 hours after cessation of alcohol and include:**

- Insomnia
- Fatigue
- Anxiety, Tremor, Restlessness
- **Palpitations**
- **Anorexia, Nausea, Vomiting**
- Headache
- **Sweating**
- **Flushing**
- Depression
- Craving

**Alcoholic hallucinosis** can appear **12-24 hours** after stopping alcohol and includes **visual**, **auditory** and **tactile** hallucinations.

**Withdrawal seizures** can appear **36 hours** after cessation and are generalised tonic-clonic seizures.

**Alcohol withdrawal delirium ('Delerium tremens') (DTs)** can appear **72 hours** after cessation.

Onset is typically **3 to 7 days after cessation** of **chronic** alcohol ingestion.

Delirium tremens, is the most severe form of alcohol withdrawal, which should be treated as a **medical emergency**.

Delirium tremens is a **hyper adrenergic state,** and is often associated with sweating, tachycardia, hyperthermia, hypertension, tachypnoea, tremor, mydirasis, visual hallucination, obtundation and confusion.

Patients at increased risk are those with a previous history of delirium tremens or alcohol withdrawal seizures, those with a co-existing infection or abnormal liver function, and older patients. It is a clinical diagnosis.

Delirium tremens should be treated with **oral lorazepam** as **first-line** treatment.

If the symptoms persist, or the medication is refused, **parenteral lorazepam**, **haloperidol** or **olanzapine** should be given. Intensive care may be required.

**Mortality without** treatment is approximately **35%,** which reduces to 5% with early recognition and treatment.

## Management:

- **Benzodiazepines** it is the **first** line of treatment for withdrawal, if no underlying structural lesion is detected and the patient does not have an epileptic disorder, **no long term antiepileptic drug therapy** is indicated.
- **Carbamazepine** at a starting dose of **800 mg** per 24 hours also effective in treatment of alcohol withdrawal.
- Phenytoin is said NOT to be as effective in the treatment of alcohol withdrawal seizures.
- **Thiamine** is also indicated in chronic alcoholism to reduce the risk of Wernicke's encephalopathy, but is not as immediately important as diazepam.

**Haloperidol** is best **avoided** because of the risk of causing **hypotension**.

Haloperidol may be used in the sedation of patients who are distressed and anxious and present a danger to themselves or others however in delirium tremens **it may lower the seizure threshold** and has no effect on the underlying pathophysiology.

**EX**: A 45-year-old man is admitted due to hematemesis. He drinks 120 units of alcohol a week. When is the peak incidence of **seizures** following alcohol withdrawal? >>> **36 hrs**.

**EX**: Male pt. admitted with **acute pancreatitis** and was being treated conservatively with IV fluids and **NPO** and was making good recovery, an arrest call was made approximately **36 hours after** his admission when he was found unconscious and in generalised tonic-clonic seizure. He eventually stopped fitting after a total of **30 mg diazepam** IVI.

What would be your next ttt of choice >>> **IV vitamin B and C (Pabrinex®)**.

The most likely cause of his seizure is **alcohol withdrawal** >>> **IV Pabrinex®** should be given to all patients with **severe alcohol withdrawal** to correct severe vitamin deficiencies and prevent Wernicke-Korsakoff syndrome.

**As** he is **no longer fitting**, continuing anti-epileptic treatment is **no** longer indicated.

The use of **phenytoin** is **not** recommended in patients with underlying liver impairment therefore **not** used in status epilepticus secondary to alcohol withdrawal.

## Alcohol - problem drinking: management

### Nutritional support:

- SIGN recommends alcoholic patients should receive **oral thiamine** if their 'diet may be deficient'

### Drugs used:

- **Benzodiazepines** for acute withdrawal.
- **Disulfram**: promotes abstinence - alcohol intake causes severe reaction due to **inhibition of acetaldehyde dehydrogenase**. Patients should be aware that even small amounts of alcohol (e.g. in perfumes, foods, mouthwashes) can produce severe symptoms. Contraindications include ischaemic heart disease and psychosis.
- **Acamprosate**: reduces craving, known to be a weak antagonist of NMDA receptors, improves abstinence in placebo controlled trials.

Alcohol is mainly metabolised in the liver to acetaldehyde by alcohol dehydrogenase.
Acetaldehyde is then oxidised to acetate by acetaldehyde dehydrogenase (AcDH).

**Alcohol** ——(Alcohol dehydrogenase)——> **Acetaldehyde** ——(Acetaldehyde dehydrogenase)——> **Acetate**

**Disulfiram Inhibits acetaldehyde dehydrogenase activity**

It irreversibly inhibits the oxidation of acetaldehyde by competing with the cofactor nicotinamide adenine dinucleotide (NAD) for binding sites on (AcDH).
The **increased acetaldehyde levels** are thought to produce the **unpleasant side effects associated with acetaldehyde syndrome** such as headaches, nausea, and flushing etcetera.
These reactions may also occur with alcohol based products, for example, **alcohol based perfumes**.
Disulfiram is **contraindicated** in **cirrhosis** and **heart** disease, and **psychosis** is a relative contraindication for its use.

**NB**: Methanol, like ethanol, is metabolised by alcohol dehydrogenase to form formaldehyde. Formaldehyde is then further metabolised by aldehyde dehydrogenase to formic acid.
Formate formation leads to a severe metabolic acidosis, and crystals forming within the eye can lead to so called **'snow field' cataract formation**.

Inhibition of metabolism of methanol by alcohol dehydrogenase with either ethanol or fomepizole is the treatment of choice.

Ethanol reduces the calcium-dependent secretion of anti-diuretic hormone (ADH) by blocking channels in the neurohypophyseal nerve terminal, so that can explains why **people who drink excessive amounts alcohol develop polyuria.**

**Ethanol inhibits ADH secretion >>> polyuria**

**Nausea** associated with hangovers is mainly due to **vagal stimulation** to the vomiting centre. Following a particular severe episode of alcohol excess people may experience tremors. These are due to increased glutamate production by neurones to compensate for the previous inhibition by ethanol.

## Wernicke's encephalopathy

Wernicke's encephalopathy is a result of **thiamine deficiency**.
Most cases occur in those with a history of **chronic alcohol ingestion** however **malnutrition** of any cause is a risk factor.

### The classic triad of features is:

- **Encephalopathy** (confusion, drowsy, disoriented,agitation)
- **Ataxia** and
- **Oculomotor dysfunction** (usually **nystagmus** but also potentially lateral rectus palsies or conjugate gaze palsies).

**Treatment:** High dose **vitamin B (Thiamine) replacement IVI** (Pabrinex)
Administration of **IV glucose** prior to giving thiamine can significantly **worsen** Wernicke's encephalopathy.

**The neurological changes are reversible if there is prompt administration of thiamine. Failure to do this results in permanent neurological disability (Korsakoff's syndrome).**

## Foetal alcohol syndrome

### It is associated with (3):

- **Mental** retardation.
- **Growth** retardation.
- **Mid-facial** abnormalities.

The foetus relies on maternal hepatic detoxification of alcohol.
Alcohol appears to cross freely between mother and foetus, yet the fetal liver has only 10% of the capacity of the adult liver to detoxify alcohol.

## Zieve's syndrome

### A combination of tetrad (4):

1) **Alcoholic hepatitis**,
2) **Jaundice**,
3) **Hyperlipidaemia**, and
4) **Haemolysis with anaemia**.

There is **no specific treatment** for Zieve's syndrome but **supportive therapy** is indicated which includes

1) Correction of clotting abnormalities.
2) Treatment of haemolysis.
3) Treating alcohol withdrawal.
4) Preventing further alcohol intake.
5) Adequate nutrition.

## St John's Wort

- St John's Wort (Hypericum perforatum), is an herbal antidepressant available over the counter (**OTC**) in the United Kingdom.
- Shown to be as effective as tricyclic antidepressants (TCA) in the treatment of **mild-moderate depression,** anxiety and sleep disturbance.
- Mechanism: thought to be **similar to SSRIs** (although **noradrenaline uptake inhibition** has also been demonstrated).
- **NICE advise 'may be of benefit in mild or moderate depression, but its use should not be prescribed or advised because of uncertainty about appropriate doses, variation in the nature of preparations, and potential serious interactions with other drugs.**

### Adverse effects:

- **Profile in trials similar to placebo.**
- Can cause **serotonin syndrome.**
- **Inducer of P450 system**, therefore decreased levels of drugs such as **warfarin**, cyclosporine. The effectiveness of the **combined oral contraceptive pill** may also be reduced.

## Theophylline

Theophylline, like caffeine, is one of the naturally occurring methylxanthines.

The main use of theophyllines in clinical medicine is as a bronchodilator in the management of asthma and COPD.

The exact mechanism of action has yet to be discovered. One theory suggests theophyllines may be a **non-specific inhibitor of phosphodiesterase** resulting in an **increase in cAMP**. Other proposed mechanisms include antagonism of adenosine and prostaglandin inhibition.

### Theophylline poisoning:

#### Features:

- Acidosis, Hypokalaemia
- Vomiting
- Tachycardia, arrhythmias
- Seizures

#### Management:

- Activated charcoal
- Charcoal haemoperfusion is preferable to haemodialysis

Theophylline is non-specific phosphodiesterase inhibitor, while sildenafil is phosphodiesterase type V inhibitor.

# Metformin

Metformin is a biguanide used mainly in the treatment of type 2 diabetes mellitus. It has a number of actions which improves glucose tolerance (see below).
Unlike sulphonylureas it does not cause hypoglycaemia and weight gain and is therefore first-line, particularly if the patient is overweight.
Metformin is also used in polycystic ovarian syndrome and non-alcoholic fatty liver disease

## Mechanism of action

- acts by **activation of the AMP-activated protein kinase (AMPK)**
- **increases insulin sensitivity**
- **decreases hepatic gluconeogenesis**
- may also reduce gastrointestinal absorption of carbohydrates

## Adverse effects

- **gastrointestinal upsets are common** (nausea, anorexia, diarrhoea), intolerable in 20%
- reduced vitamin B12 absorption - rarely a clinical problem
- **lactic acidosis** with severe liver disease or renal failure
  - it is now increasingly recognised that lactic acidosis secondary to metformin is rare, although it remains important in the context of exams

## Contraindications

- **chronic kidney disease**: NICE recommend that the dose should be reviewed if the creatinine is > 130 µmol/l (or eGFR < 45 ml/min) and stopped if the creatinine is > 150 µmol/l (or eGFR < 30 ml/min)
- metformin may cause lactic acidosis if taken during a period where there is tissue hypoxia. Examples include a **recent myocardial infarction**, sepsis, acute kidney injury and severe dehydration
- iodine-containing x-ray contrast media: examples include peripheral arterial angiography, coronary angiography, intravenous pyelography (IVP); there is an increasing risk of provoking renal impairment due to contrast nephropathy; metformin should be discontinued on the day of the procedure and for 48 hours thereafter
- alcohol abuse is a relative contraindication

## Starting metformin

- metformin should be **titrated up slowly** to reduce the incidence of gastrointestinal side-effects
- **if patients develop unacceptable side-effects then modified-release metformin should be considered**

## Prescribing in patients with heart failure

### The following medications may exacerbate heart failure:

- **thiazolidinediones**
  - pioglitazone is contraindicated as it causes fluid retention
- **verapamil**
  - negative inotropic effect
- **NSAIDs/glucocorticoids**
  - should be used with caution as they cause fluid retention
  - low-dose aspirin is an exception - many patients will have coexistent cardiovascular disease and the benefits of taking aspirin easily outweigh the risks
- **class I antiarrhythmics**
  - flecainide (negative inotropic and proarrhythmic effect)

## Prescribing in patients with renal failure

Questions regarding which drugs to avoid in renal failure are common

### Drugs to avoid in renal failure

- antibiotics: tetracycline, nitrofurantoin
- NSAIDs
- lithium
- metformin

### Drugs likely to accumulate in chronic kidney disease - need dose adjustment

- most antibiotics including penicillins, cephalosporins, vancomycin, gentamicin, streptomycin
- digoxin, atenolol
- methotrexate
- sulphonylureas
- furosemide
- opioids

### Drugs relatively safe - can sometimes use normal dose depending on the degree of chronic kidney disease

- antibiotics: erythromycin, rifampicin
- diazepam
- warfarin

## Teratogens

The following table includes some of the drugs and medical conditions that may harm a developing fetus:

| Drug/condition | Effect |
|---|---|
| ACE inhibitors | Renal dysgenesis<br>Craniofacial abnormalities |
| Alcohol | Craniofacial abnormalities |
| Aminoglycosides | Ototoxicity |
| Carbamazepine | Neural tube defects<br>Craniofacial abnormalities |
| Chloramphenicol | 'Grey baby' syndrome |
| Cocaine | Intrauterine growth retardation<br>Preterm labour |
| Diethylstilbesterol | Vaginal clear cell adenocarcinoma |
| Lithium | Ebstein's anomaly (atrialized right ventricle) |
| Maternal diabetes mellitus | Macrosomia<br>Neural tube defects<br>Polyhydramnios<br>Preterm labour<br>Caudal regression syndrome |
| Smoking | Preterm labour<br>Intrauterine growth retardation |
| Tetracyclines | Discoloured teeth |
| Thalidomide | Limb reduction defects |
| Valproate | Neural tube defects<br>Craniofacial abnormalities |
| Warfarin | Craniofacial abnormalities |

# Drug toxicity and poisoning

## Ethylene glycol toxicity

Ethylene glycol is a type of alcohol used as a **Coolant** or **Antifreeze** used in cars.

**Features of toxicity are divided into 3 stages:**

**Stage 1**: Symptoms **similar to alcohol intoxication**: **confusion**, **coma**, slurred speech, dizziness.

**Stage 2**: **Severe metabolic acidosis with high anion gap and high osmolar gap, hyperventilation, kussmaul breathing, hypocalcaemia**. Also **Tachycardia**, **Hypertension**.

**Stage 3**: **Acute renal failure** (caused by **oxalate crystalluria**).

Ethylene glycol intoxication presents with DCL, severe high anion gap metabolic acidosis, renal, respiratory, cardiac failure.

**Multi-organ failure** is thought to occur at least in part due to widespread deposition of **calcium oxalate crystals** around 12 hrs after the initial insult.

Because of the possible formation of calcium oxalate, **calcium** level should be assessed.

Unfortunately with delayed presentation, ingestion of **relatively small amount** of ethylene glycol as little as **30 ml** is **fatal**.

Symptoms are: nausea, vomiting, convulsions, coma and respiratory distress with **no alcohol odour on the breath**. This differentiates ethylene glycol poisoning from other alcohols such as ethanol or methanol.

An **osmolar gap** exists when **measured** plasma osmolality is **greater than calculated** osmolality by **> 10** mOsmol/kg.

**Calculated osmolality = 2(Na + K) + urea + glucose**.

Several unmeasured osmotically active substances in the plasma such as ethanol. Methanol, ethylene glycol, mannitol and glycine are responsible for increased osmolar gap.

## Management has changed in recent times:

- **Ethanol** has been used for many years:
  a. Works as a **competitive inhibitor** with ethylene glycol **for the enzyme alcohol dehydrogenase.**
  b. This limits the formation of toxic metabolites (e.g. glycoaldehyde and glycolic acid) which are responsible for the haemodynamic/metabolic features of poisoning.
- **Fomepizole (4-methyl pyrazole)**, a **competitive inhibitor of alcohol dehydrogenase**, is now used **first-line in preference to ethanol.**
- **Haemodialysis** also has a role in refractory cases of metabolic acidosis and acute renal failure.

**Fomepizole** is now used as the **first** line of ttt rather than ethanol in ethylene glycol toxicity. **Haemodialysis** is indicated **only in** refractory cases of metabolic acidosis and acute renal failure.

**N.B**: Loss of vision is seen in methanol rather than ethylene glycol poisoning

**EX**: 40 year old mechanic was bought unconscious to ER, he was found at the **garage** he owns by his wife having an **epileptic** fit with vomiting, he is previously fit and well, **no smell of alcohol**, Lab: **metabolic acidosis**, **hypocalcaemia**, **high serum osmolality**, **urine: oxalate crystals** >>> **Ethylene glycol poisoning**.

## Methanol poisoning

Methanol is sometimes used as a substitute for Ethanol by alcoholics, as it similarly causes inebriation.

Usually seen with **middle-aged homeless man**

Methanol poisoning causes both the effects associated with alcohol (intoxication, nausea etc.) and also specific visual problems, including **blindness**. These effects are thought to be secondary to the **accumulation** of **formic acid**.

Formic acid later produces a **metabolic acidosis** and **retinal injury**.

The actual pathophysiology of methanol-associated visual loss is not fully understood but it is thought to be caused by a form of **optic neuropathy**.

### Management:

- Fomepizole **IV** or **Ethanol IV**
- **Haemodialysis:** Indications for **hemodialysis** in methanol poisoning include:
  - Low GCS level which points to a severe overdose.
  - A methanol level > 0.5g/L.
  - Renal impairment.
  - Any visual disturbance.

**Fomepizole** - used in ethylene glycol and methanol poisoning - **competitive inhibitor of alcohol dehydrogenase**

## Ecstasy poisoning

Ecstasy (**MDMA**, 3,4-Methylenedioxymeth**amphetamine**) use became popular in the 1990's during the emergence of **dance music culture at night clubbing**.

### Clinical features:

- **Neurological**: DCL, agitation, anxiety, confusion, ataxia. Dilated pupils
- **DIC (↓ PLT)** and **Rhabdomyolysis (↑CPK) >> renal failure**
- **Cardiovascular**: **tachycardia**, hypertension
- Hyper**thermia** and Hyper**ventilation**
- Hypo**natraemia**

Ecstasy is thought to stimulate the production of anti-diuretic hormone **ADH**. Users of ecstasy also commonly drink too much water in the (mistaken) belief that this will protect them from the adverse effects.

### Management:

- Supportive: ABC, BDZ for control of seizure, Na Nitroprusside for HTN, urinary alkalinisation for ↓ progression of ARF.
- **Dantrolene IV** may be used for hyperthermia if simple measures fail.

# Cocaine

Cocaine is an alkaloid derived from the coca plant.
It is widely used as a recreational stimulant.
The price of cocaine has fallen sharply in the past decade resulting in cocaine toxicity becoming a much more frequent clinical problem.
This increase has made cocaine a favourite topic of question writers.

**Mechanism of action:** Cocaine blocks the uptake of dopamine, noradrenaline and serotonin.
The use of cocaine is associated with a **wide variety of adverse effects:**

**Cardiovascular effects:**

- **Hypertension**
- Both **tachycardia** and bradycardia may occur
- Myocardial infarction
- Aortic dissection
- QRS widening and QT prolongation

**Neurological effects:**

- Mydriasis
- Hypertonia
- Hyperreflexia
- **Seizures**

**Psychiatric effects:**

- Agitation
- Hallucinations
- **Psychosis**

**Others:**

- **Hyperthermia**
- **Rhabdomyolysis**
- **Metabolic acidosis**
- **Renal failure**

**Management of cocaine toxicity:**

- In general **benzodiazepines IV** are generally first-line for most cocaine related problems.
- Chest pain: **benzodiazepines** + **glyceryl trinitrate**. If myocardial infarction develops then primary PCI.
- Hypertension: **benzodiazepines** + **sodium nitroprusside.**

The use of beta-blockers in cocaine-induced cardiovascular problems is a controversial issue.
The American Heart Association issued a statement in 2008 warning against the use of beta-blockers (due to the risk of unopposed alpha-mediated coronary vasospasm) but many cardiologists since have questioned whether this is valid.
If a reasonable alternative is given in an exam it is probably wise to choose it

## Iron tablets overdose

**C/P:** Circulatory collapse (hypotension), abdominal pain, coffee ground vomiting, black stool.
**Raised bicarbonate** and **low potassium** are more consistent with a metabolic alkalosis secondary to vomiting.

### Treatment:

- Activated charcoal is NOT used as it is a very poor adsorber to iron.
- **Gastric lavage** is indicated with instillation of Desferrioxamine into the stomach to reduce further iron absorption.
- **Desferrioxamine IV** at rate 15mg/kg/hr is an **initial** ttt of choice and it is important to start with it as early as possible.
- If hypotension/circulatory collapse is not present then it may be given **IM** at the rate of 2 gm every 6-12 hours.
- Haemodialysis
- Plasma exchange

**Iron tablets** are **radiopaque** and thus may be visualised on **plain films** (a number of small radiopaque shadows in the centre of the abdomen) or CT.

## Cyanide poisoning

Cyanide may be used in **insecticides, photograph development, fire/ burning of polyurethane foams in factory or house (fireman)** and the production of certain metals.

Toxicity results from irreversible inhibition of cellular oxidising enzymes (irreversible blocking mitochondrial energy transport).

Cyanide causes the **inhibition** of the enzyme **cytochrome oxidase C** which is an essential part of the mitochondrial electron transfer chain (ETC). It therefore interferes with the basic process of **cellular respiration**, preventing the formation of ATP and causing rapid cell death.

### Presentation:

- 'Classical' features: **Brick-red skin**, smell of bitter almonds.
- Acute:
  - Early: **hypoxia, hypotension, headache, confusion, chest tightness.**
  - Late: **pulmonary oedema**, cardiovascular collapse, **respiratory arrest**, apnoea, paralysis and **death** within few minutes.
- Chronic: ataxia, peripheral neuropathy, dermatitis.

## Management:

- Supportive measures: 100% oxygen
- Patient should be **intubated and ventilated**.
- Definitive: **Hydroxocobalamin IV (Dicobalt edetate IV:** 300 mg over 1 min, which can be repeated 3 times depending on the response),
- Alternatives includes: **amyl nitrite (inhaled), sodium nitrite (IV), and sodium thiosulfate (IV).**

Cyanide poisoning >>> the antidote of choice is **Dicobalt edetate IVI**

Mouth to mouth resuscitation should **NOT** be attempted where there is a suspicion of cyanide exposure, due to risks to the resuscitators.
**EX:** Pt at ICU has severe hypertension on **Na Nitroprusside** and he is stable, after a few hours later he, just after the **nursing shift change**, he has become acutely confused, SOB, central chest pain, abdominal pain, vomiting, BP 100/60 mmHg, PH 7.1, metabolic acidosis, widespread ST depression consistent with myocardial ischaemia >>> **Cyanide poisoning** may be due to uncover of Na Nitroprusside so **it degrades in sunlight to form cyanide** >>> **treatment**: **Dicobalt edetate** 300 mg IV bolus and can be repeated 3 times, **Nitrate** is an alternative potential for cyanide poisoning if edetate is unavailable.

# Organophosphate insecticide poisoning

Usually occurs in **farmers** or **gardener**.
Example: **Malathion** and **Parathion**.
One of the effects of organophosphate poisoning is **irreversible inhibition of acetyl cholinesterase. (So ↑ Ach).**
**Features** can be predicted by the accumulation of **acetylcholine** (mnemonic = **SLUDGE**):

1) **S**alivation
2) **L**acrimation
3) **U**rination
4) **D**efecation/diarrhoea
5) **G**astrointestinal symptoms
6) **E**mesis.
7) Cardiovascular: **hypotension, bradycardia**
8) Also: **miosis, muscle fasciculation**

**Clinical manifestations may be classified into muscarinic, nicotinic and CNS effects, as follow:**

- **Muscarinic**: vomiting, diarrhoea, excessive salivation, sweating, severe diaphoresis, abdominal cramps, bronchospasm, miosis, bradycardia.
- **Nicotinic**: muscle fasciculations, tremors, weakness and death is usually caused by respiratory muscles paralysis.
- **CNS**: agitation, seizures, confusion, coma.

**BP and pulse may be decrease due to muscarinic effects, or increased due to nicotinic effects.**

**Management:**

- **Atropine IV:** it may reverse the **muscarinic** effects, but not the nicotinic effects.
- Supportive measures: **intubation and MV.**
- Decontamination of skin and clothes, and reduction of enteral absorption with activated charcoal may be used.
- The role of **Pralidoxime** is a cholinesterase activator, it is a specific antidote that acts to regenerate the enzyme activity at all affected sites – it should be given as soon as possible in addition to atropine.

## Arsenic poisoning

The combination of **mixed sensorimotor polyneuropathy** in the presence of possible exposure to pesticides in a **farmer** would suggest a diagnosis of chronic arsenic poisoning.
The transverse white lines on the finger nails are **Mees' lines.**

**NB:** Lead poisoning gives a predominantly motor neuropathy.

## Mercury poisoning

**Features:**

1) **Paraesthesia**
2) **Visual field defects**
3) **Hearing loss**
4) **Irritability**
5) **RTA** (Renal tubular acidosis)

**Treatment:** Chelation therapy for acute inorganic mercury poisoning can be done with **DMSA** (2,3 dimercapto-1-propanesulfonic acid) which is FDA-approved.

However, several studies found that no clear clinical benefit from DMSA treatment for poisoning due to mercury vapour.

**No** chelator for methyl-mercury or ethyl-mercury is approved by the FDA. DMSA is the most frequently used for severe methyl-mercury poisoning, as it is given orally, has fewer side effects.

## Botulinum toxin (Botox)

As well as the well-publicised cosmetic uses of Botulinum toxin ('Botox') there are also a number of licensed indications:

1) **Blepharospasm**
2) **Hemi facial spasm**

# Carbon monoxide poisoning

Carbon monoxide has a high affinity for haemoglobin and myoglobin resulting in a left-shift of the oxygen dissociation curve and tissue hypoxia.
There are approximately 50 per year deaths from accidental carbon monoxide poisoning in the UK.

**Pathophysiology: in carbon monoxide poisoning the oxygen saturation of haemoglobin decreases leading to an early plateau in the oxygen dissociation curve Questions may hint at badly maintained housing e.g. student houses.**

## Features of carbon monoxide toxicity

- **headache: 90% of cases**
- nausea and vomiting: 50%
- vertigo: 50%
- confusion: 30%
- subjective weakness: 20%
- severe toxicity: 'pink' skin and mucosae, hyperpyrexia, arrhythmias, extrapyramidal features, coma, death

## Investigations

- pulse oximetry may be falsely high due to similarities between **oxyhaemoglobin and carboxyhaemoglobin**
- therefore a venous or arterial blood gas should be taken
- typical carboxyhaemoglobin levels
  - < 3% non-smokers
  - < 10% smokers
  - 10 - 30% symptomatic: headache, vomiting
  - > 30% severe toxicity
- an ECG is a useful supplementary investgation to look for cardiac ischaemia

## Management

- **patients** with suspected carbon monoxide poisoning should be assessed in the emergency department
- 100% high-flow oxygen via a non-rebreather mask
  - from a physiological perspective, this decreases the half-life of carboxyhemoglobin (COHb)
  - should be administered as soon as possible, with treatment continuing for a minimum of six hours
  - target oxygen saturations are 100%
  - treatment is generally continued until all symptoms have resolved, rather than monitoring CO levels

- **hyperbaric oxygen**
  - due to the small number of cases the evidence base is limited, but there is some evidence that long-term outcomes may be better than standard oxygen therapy for more severe cases
  - therefore, discussion with a specialist should be considered for more severe cases (e.g. levels > 25%)
  - in 2008, the Department of Health publication 'Recognising Carbon Monoxide Poisoning' also listed loss of consciousness at any point, neurological signs other than headache, myocardial ischaemia or arrhythmia and pregnancy as indications for hyperbaric oxygen

## Caustic substance ingestion

Caustic (corrosive) substance ingestion is a common emergency department presentation in adults and children. The majority of cases are accidental exposures to household products: these are usually of little clinical consequence. Conversely, significant morbidity can occur when the substance is consumed in larger quantities with the intention of deliberate self-harm.

### Types of substance* - vital to obtain bottle/label if possible

- Oxidising agents, e.g. hydrogen peroxide, sodium hypochlorite (found in household bleach)
- Strong alkali, e.g. sodium hydroxide, potassium hydroxide (found in dishwasher cleaner, industrial cleaners) -> liquefactive necrosis, more commonly resulting in oesophageal injury
- Strong acid, e.g. hydrochloric, nitric acid (found in car batteries, WC cleaner) -> coagulative necrosis, more commonly resulting in gastric injury

**Acute management 1** - (general principles, local guidance on timing of endoscopy and PPI may vary)

- ABCDE approach, particular caution to airway swelling and compromise, look for peri-oral oedema
- Urgent upper GI surgical referral if signs of perforation present (surgical emphysema, mediastinal widening on chest x-ray)
- **Neutralisation** of ingested substance (e.g. with milk) should be avoided as the resulting exothermic reaction will release heat and may cause further injury
- High dose IV PPI
- Symptomatic ingestion (drooling, vomiting, dysphagia, odynophagia, chest pain) requires urgent assessment with upper GI endoscopy to

assess the degree of ulceration (Zargar classification). Extensive injury on endoscopy should prompt consideration of urgent surgical exploration
- Asymptomatic ingestion can usually be discharged after a trial of oral fluid and a period of observation

## Complications

**Acute**

- Upper GI ulceration, perforation
- Upper airway injury and compromise
- Aspiration pneumonitis
- Infection
- Electrolyte disturbance (e.g. hypocalcaemia in hydrofluoric acid ingestion)

**Chronic**

- Strictures, fistulae, gastric outlet obstruction
- **Upper GI carcinoma (estimated 1000-3000 fold increased risk)**

*Please refer to National Poisons Information/toxbase for specific management

# Oculogyric crisis

An oculogyric crisis is an **acute dystonic reaction** to certain drugs or medical conditions due to **dopaminergic blockade** at the basal ganglion.

The effects usually occur within 72 hours but have been reported to occur within 30 minutes of starting treatment.

It is a form of **extrapyramidal** disorder.

**EX:** Abnormal head movements and has gone 'cross-eyed'. The neck is extended and positioned to the right. The eyes are deviated upwards and are slightly converged.

## Features:

- **Restlessness, agitation**
- Involuntary **upward deviation of the eyes**

## Causes:

- Phenothiazines
- Haloperidol
- **Metoclopramide**
- Post encephalitic Parkinson's disease

**Management:** Although **self-limiting**, the reaction can be reversed by:

- **Procyclidine HCL**
- **Trihexyphenidyl HCL** (formerly known as Benzhexol)
- **Benztropine IV (Cogentin 2mg ®)**
- **Diphenhydramine** is alternative option.

## Beta-blocker overdose

**Features:**

- Bradycardia
- Hypotension
- Heart failure
- Syncope

**Management:**

1) If symptomatic bradycardia then **atropine** should be used in the **first** instance.
2) In resistant cases to atropine: **glucagon IV (50-150 Mcg/Kg)** followed by **IV infusion** may be used:
   a. Glucagon can be effective but this should be tried after atropine.
   b. Glucagon has a **positive inotropic action** on the heart by raising the myocardial cAMP levels, and
   c. **It decreases ↓ renal vascular resistance.**

   d. So Glucagon is useful in patients with beta-blocker Cardiotoxicity.
3) **Cardiac pacing** should be **reserved** for patients **unresponsive** to pharmacological therapy.
4) Haemodialysis is **not** effective in beta-blocker overdose.
5) If taken within **one hour** of presentation, **activated charcoal** should be tried.

Beta-blocker overdose management >> **Atropine IV + Glucagon IV**

Doses of glucagon used are much higher than those conventionally used for reversing hypoglycaemia in diabetes, it is a **bolus of 3-10 mg** being required, **then 2-5 mg/hr by infusion.**

# Overdose and poisoning: management

**The table below outlines the main management for common overdoses:**

| Toxin | Treatment |
|---|---|
| **Paracetamol** | Management<br>• activated charcoal if ingested < 1 hour ago<br>• N-acetylcysteine (NAC)<br>• liver transplantation |
| **Salicylate** | Management<br>• urinary alkalinization with IV bicarbonate<br>• haemodialysis |
| **Opioid/opiates** | Naloxone |
| **Benzodiazepines** | Flumazenil<br>The majority of overdoses are managed with supportive care only due to the risk of seizures with flumazenil. It is generally only used with severe or iatrogenic overdoses. |
| **Tricyclic antidepressants** | Management<br>• IV bicarbonate may reduce the risk of seizures and arrhythmias in severe toxicity<br>• arrhythmias: class 1a (e.g. Quinidine) and class Ic antiarrhythmics (e.g. Flecainide) are contraindicated as they prolong depolarisation. Class III drugs such as amiodarone should also be avoided as they prolong the QT interval. Response to lignocaine is variable and it should be emphasized that correction of acidosis is the first line in management of tricyclic induced arrhythmias<br>• dialysis is ineffective in removing tricyclics |
| **Lithium** | Management<br>• mild-moderate toxicity may respond to volume resuscitation with normal saline<br>• haemodialysis may be needed in severe toxicity<br>• sodium bicarbonate is sometimes used but there is limited evidence to support this. By increasing the alkalinity of the urine it promotes lithium excretion |
| **Warfarin** | Vitamin K, prothrombin complex |
| **Heparin** | Protamine sulphate |

| Toxin | Treatment |
|---|---|
| **Beta-blockers** | Management<br>• if bradycardic then **atropine**<br>• in resistant cases **glucagon** may be used |
| **Ethylene glycol** | Management has changed in recent times<br>• ethanol has been used for many years<br>• works by competing with ethylene glycol for the enzyme alcohol dehydrogenase<br>• this limits the formation of toxic metabolites (e.g. Glycoaldehyde and glycolic acid) which are responsible for the haemodynamic/metabolic features of poisoning<br>• **fomepizole**, an inhibitor of alcohol dehydrogenase, is now used first-line in preference to ethanol<br>• haemodialysis also has a role in refractory cases |
| **Methanol poisoning** | Management<br>• fomepizole or ethanol<br>• haemodialysis |
| **Organophosphate insecticides** | Management<br>• **atropine**<br>• the role of pralidoxime is still unclear - meta-analyses to date have failed to show any clear benefit |
| **Digoxin** | Digoxin-specific antibody fragments |
| **Iron** | **Desferrioxamine**, a chelating agent |
| **Lead** | **Dimercaprol, calcium edetate** |
| **Carbon monoxide** | Management<br>• **100% oxygen**<br>• **hyperbaric oxygen** |
| **Cyanide** | **Hydroxocobalamin**; also combination of amyl nitrite, sodium nitrite, and sodium thiosulfate |

# Anaphylaxis

**Common identified causes of anaphylaxis:**

- Food (e.g. **Nuts**) - the most common cause in children
- Drugs
- Venom (e.g. Wasp sting)

Anaphylaxis may be defined as a severe, life-threatening, generalised or systemic hypersensitivity reaction.

Anaphylaxis is one of the few times when you would not have time to look up the dose of a medication.

The Resuscitation Council guidelines on anaphylaxis have recently been updated.

**Adrenaline IM or SC** is by far the most important drug in anaphylaxis and should be given **as soon as possible**.

The Resuscitation Council guidelines **only** recommend giving **adrenaline intramuscularly**, regardless of whether the patient has IV access or not.

Adrenaline **can be repeated every 5 minutes** if necessary.

The best site for **IM** injection is the **anterolateral aspect of the middle third of the thigh.**

The recommended doses for adrenaline, hydrocortisone and chlorphenamine are as follows:

| | Adrenaline (1 in 1000) | Hydrocortisone | Chlorphenamine |
|---|---|---|---|
| **< 6 months** | 150 mcg (0.15ml) | 25 mg | 250 mcg/kg |
| **6 months - 6 years** | 150 mcg (0.15ml) | 50 mg | 2.5 mg |
| **6-12 years** | 300 mcg (0.3ml) | 100 mg | 5 mg |
| **Adult and child > 12 yrs.** | 500 mcg (**0.5ml**) | **200 mg** | **10 mg** |

**Anaphylaxis** >>> **Serum mast cell Tryptase** levels **rise** following an acute episode within 1-2 hours and may remain elevated for up to 12 hours following an acute episode of anaphylaxis. (**NOT** IgE, plasma histamine nor Basophil count).

**Mast cell tryptase** is the preferred measure test for mast cell degranulation.

**Current UK resuscitation guidelines suggest adrenaline only if there is:**

- **Stridor**
- **Wheeze**
- **Respiratory distress**, or
- **Clinical evidence of shock**

# Salicylate overdose

A key concept for the exam is to understand that salicylate overdose leads to a **mixed respiratory alkalosis and metabolic acidosis.**

**Early** stimulation of the respiratory centre leads to a **respiratory alkalosis** whilst **later** the direct acid effects of salicylates (combined with acute renal failure) may lead to a **metabolic acidosis**.

In children metabolic acidosis tends to predominate.

## Features:

- Hyperventilation (centrally stimulates respiration).
- **Sweating** and **pyrexia**: as salicylates cause the **uncoupling of oxidative phosphorylation** leading to ↓ **ATP production**, ↑ oxygen consumption and ↑CO2 and heat production.
- Nausea/vomiting, occasionally haematemesis.
- Hyperglycaemia and hypoglycaemia.
- **Tinnitus**.
- Pancreatitis
- ARF
- Lethargy.
- Encephalopathy and Seizures.
- Coma.

## Treatment:

- General: (ABC and **multiple-dose activated charcoal** used be given **even up to 12 hrs after overdose ingestion,** as there is decreased gastric emptying with salicylates. Although most UK guidelines only recommend its use **within the first hour** of salicylate ingestion).
- Urinary alkalinization to raise PH of urine from 5 to 8 by **IV NaHCO3,** will increase the excretion of the acid 10-fold: It is **now rarely used,** it is **contraindicated** in **cerebral** and **pulmonary oedema** with most units now proceeding straight to haemodialysis in cases of severe poisoning. There is no value in forced diuresis.
- **Haemodialysis**.

**Indications for haemodialysis in salicylate overdose:**

- **Serum concentration > 700 mg/dl** (5 mmol/litre)
- Acute renal failure
- Metabolic acidosis resistant to treatment
- Pulmonary oedema
- Neurological impairment: (Seizures, Coma or hallucinations)

The **mixed** respiratory alkalosis and metabolic acidosis (**normal or high pH**) in a sweaty, confused patient point towards salicylate overdose. The development of pulmonary oedema suggests severe poisoning and is an indication for haemodialysis

## Paracetamol overdose: management

Paracetamol can cause liver failure even at relatively low doses (over 7 grams).
A dose of more than 150 mg/kg is considered to be toxic and toxicity occurs at a lower concentration if the patient is thought to be in high risk group.

### Management:

The following is based on 2012 Commission on Human Medicines (CHM) review of paracetamol overdose management.

The big change in these guidelines was the removal of the 'high-risk' treatment line on the normogram. **All patients are therefore treated the same regardless of risk factors for hepatotoxicirt.**

The National Poisons Information Service/TOXBASE should always be consulted for situations outside of the normal parameters.

Paracetamol levels should be carried out at 4 hours not earlier than that.

### Acetylcysteine IVI (Parvolex ®) should be given if:

- There is **a staggered overdose** (an overdose is considered staggered if all the tablets were not taken within 1 hour); or
- There is **doubt over the time of paracetamol ingestion, regardless** of the plasma paracetamol concentration; or
- **The plasma paracetamol concentration** is **on or above a single treatment line** joining points of **100 mg/L at 4 hours** and **15 mg/L at 15 hours, regardless** of risk factors of hepatotoxicity.

**Acetylcysteine IVI** is **now infused over 1 hour** (rather than the previous 15 minutes) to reduce the number of adverse effects.
**Adverse reactions to IV infusion** are seen in about **15%** of individuals in the form of **facial flushing**, **pruritis** and **rash**.
**Treatment:** of this adverse reactions is: **stop the IV infusion for a short period**, give **anti-histaminic** and then **re-start the IV infusion at half rate**.
The benefit of NAC is maximum **as long as it is given within 8 hours** of ingestion. Its benefit **extends up to 24 - 36 hours following ingestion**.

The **liver normally conjugates paracetamol** with **glucuronic acid/sulphate** which are then excreted in the urine.

**In** an **overdose** the **conjugation system becomes saturated** leading to oxidation by P450 mixed function oxidases*. This produces **a toxic metabolite (N-acetyl-B-benzoquinone imine) (NABQI)** and the drug is then **conjugated with glutathione**.

Normally **glutathione** acts as a defence mechanism by **conjugating** with the **toxin** forming **the non-toxic mercapturic acid**.

If glutathione stores run-out, the toxin forms covalent bonds with cell proteins, denaturing them and leading to cell death. This occurs not only in **hepatocytes** but also in the **renal** tubules.

**N-acetyl cysteine** and **methionine** replenish glutathione stores in the liver so used in the management of paracetamol overdose as it is a **precursor of glutathione** and hence can **increase hepatic glutathione production.**

**Methionine orally** can be used in patients allergic to NAC.

Renal damage may occur by the same way, owing to renal P450 metabolism.

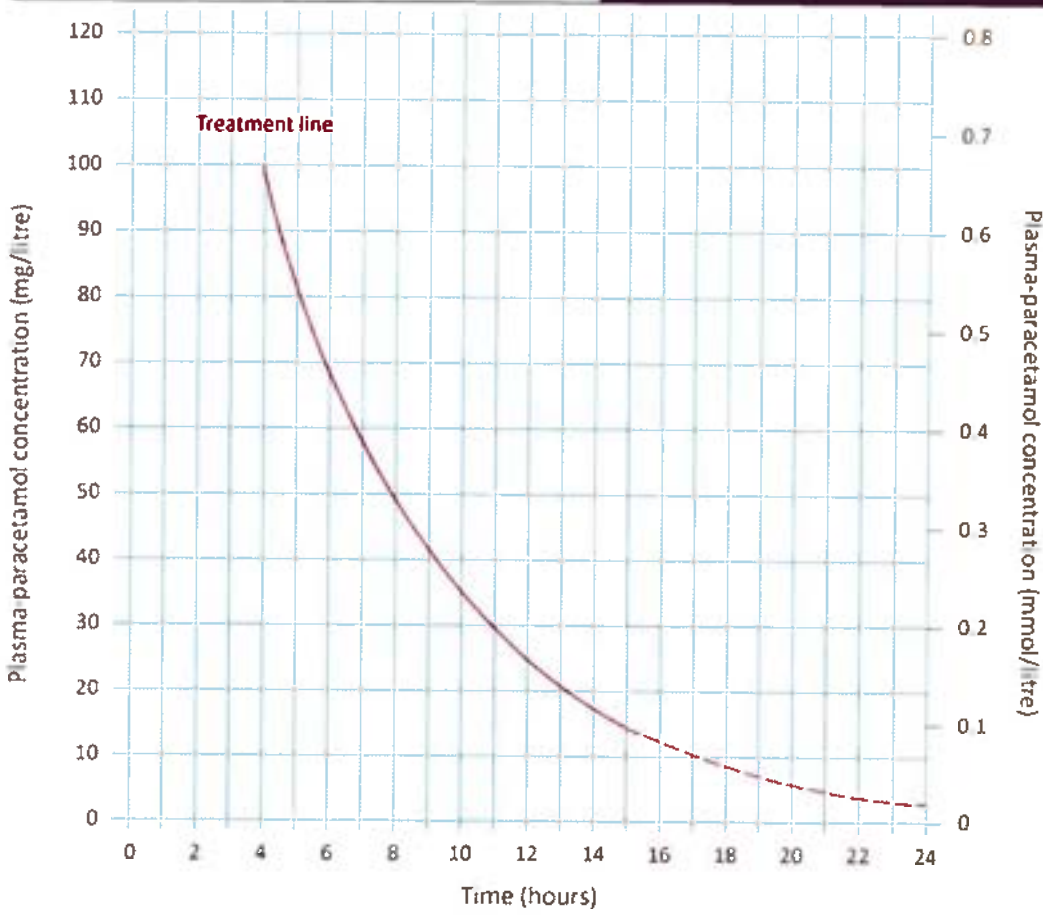
*this explains why there is a lower threshold for treating patients who take P450 inducing medications e.g. Rifampicin or Phenytoin or Carbamazepine.

**The following patients are at ↑ risk of developing hepatotoxicity following a paracetamol overdose:**

- **Anorexia nervosa (↓ glutathione stores)**.
- **Alcoholics**.
- P450 enzyme **inducers** like: Rifampicin, Phenytoin, St John's Wort or Carbamazepine.
- **HIV**.

It is true that tobacco smoking induces CYP1A2 (one of the P450 enzymes). However, it is **not** currently included in the list of high-risk situations.

It is unusual to see severe hypotension in paracetamol overdose but is feasible in **a massive overdose** and usually associated with **lactic acidosis** so **first immediate** step in the management is **IV fluids NOT** NAC IV.




**King's College Hospital criteria for liver transplantation (paracetamol-induced acute liver failure):**
**Arterial pH < 7.3, 24 hours after ingestion**
**OR arterial lactate > 3 mmol/L after adequate fluid resuscitation.**
**OR ALL 3 of the following occur in a 24 hr period:**

- **Prothrombin time > 100 seconds (INR > 6.5).**
- **Creatinine > 300 µmol/l.**
- **Grade III or IV encephalopathy.**

**INR** as an indicator of hepatic synthetic function is **the best marker of severity** of paracetamol overdose at this stage.
**INR >2.0** at or before 48 hours or **>3.5** at or before 72 hours should prompt referral to a specialist unit.
Peak elevation occurs around 72-96 hours.
Serum **bilirubin** > 300 µmol/L is part of the selection criteria for liver transplantation in **non**-paracetamol induced acute liver failure.

- **King's College Hospital** criteria for liver transplantation (in non-paracetamol related liver failure): (like food e.g. mushroom)
- INR greater than 6.5; OR

**Three of the following 5 criteria:**

- Patient age of less than 11 or greater than 40.
- Serum bilirubin greater than 300 Mmol/L.
- Time from onset of jaundice to the development of coma > 7 days.
- INR greater than 3.5
- Drug toxicity, regardless whether it was the cause of the acute liver failure.

## Reye's syndrome

It is the **rarely** occurring **triad** of **encephalopathy**, **fatty liver degeneration** and **elevated transaminases** during a **post-infectious periods**.

It occurs predominantly in patients **under the age of 18 years** and may commonly **follow influenza or varicella infection**.

Case **fatality** rate is **very high** at between **25-50% of patients**.

The key factor in avoiding the syndrome is **the cessation of aspirin use in children.**

Unfortunately there is **no** specific antidote and ttt is supportive, a key factor being recognition and ttt of raised intracranial pressure.

**EX**: **16** years girl has **chicken pox** from nursery contact and has received cold preparation containing **aspirin** & paracetamol then she developed persistent **vomiting**, **confusion**, generalized tonic-clonic **seizures**, hepatomegaly, ↑ **ALT** 570, and ↑ **AST** 460, ↑**Bilirubin** 85 Mmol/L >>> **Reye's syndrome**.

3) Focal spasticity including cerebral palsy patients, hand and wrist disability associated with stroke
4) Spasmodic torticollis
5) Severe hyperhidrosis of the axillae
6) Achalasia

# Medical conditions

## Motion sickness

Motion sickness describes the nausea and vomiting which occurs when an apparent discrepancy exists between visually perceived movement and the vestibular systems sense of movement.

### Management:

- The BNF recommends **hyoscine** (e.g. transdermal patch) as being the most effective treatment. Use is limited due to side-effects.
- Non-sedating antihistamines such as **cyclizine** or **cinnarizine** are recommended in preference to sedating preparation such as promethazine.

Motion sickness: **Hyoscine** > **cyclizine** or **cinnarizine** > promethazine

## Eclampsia

**Eclampsia may be defined as the development of seizures in association pre-eclampsia. To recap, pre-eclampsia is defined as:**

- Condition seen **after 20 weeks gestation**
- **Pregnancy-induced hypertension (PIH)**
- **Proteinuria**

**Magnesium sulphate** is used to both **prevent** seizures in patients with severe pre-eclampsia and **treat** seizures once they develop.

**Guidelines on its use suggest the following:**

- It should be given **once** a decision to deliver has been made.
- In eclampsia an **IV bolus of 4g over 5-10 minutes** should be given followed by an **infusion of 1g / hour.**
- Treatment **should continue for 24 hours after** last seizure or delivery (around 40% of seizures occur post-partum)
- **Urine output**, **reflexes**, **respiratory rate** and **oxygen saturations** should be monitored during treatment.

MgSO4 IVI >>>> Monitor >>>> UOP+ Reflexes + RR + O2 Sat %

Other important aspects of treating severe pre-eclampsia/eclampsia include **fluid restriction** to avoid the potentially serious consequences of fluid

overload like Pulmonary and cerebral oedema which are important causes of morbidity and mortality in severe pre-eclampsia.

Severe pre-eclampsia >>> **Restrict fluids**

NICE are very clear on this point: '**Offer antihypertensive drug treatment to women of child-bearing potential in line with the recommendations on Management of pregnancy with chronic hypertension'.**

**EX: Methyldopa, Hydralazine, Labetalol and Nifedipine.**

## DRESS syndrome

DRESS is an unexpected, severe reaction to medication. Several organs are commonly affected including the skin, liver, kidneys, lungs and heart. Not all of these organs may be affected at any one time.

Classically patients develop a morbilliform **skin rash in 80% cases which often leads to an exfoliative dermatitis, high fever, and inflammation of one or more** organs. Vesicles and bullae may be seen. Erythroderma can occur in 10% of cases, mucosal involvement in 25% and facial swelling in 30%. The reaction usually occurs 2-8 weeks after commencing the offending drug.

**Patients may develop systematic symptoms** which can include haematological abnormalities (raised and low white count, eosinophilia (in 30% this is > 2.0 * $10^9$ /L, thrombocytopaenia, anaemia, atypical lymphocytes), enlarged lymph nodes (75%), 10% develop kidney disease which is usually mild (interstitial nephritis is common, renal failure is rare), myocarditis, pericarditis, liver enlargement, hepatitis and rarely hepatic necrosis with liver failure (abnormal liver function tests are found in 70-90% in particularly raised transaminases), lung disease (pneumonitis, pleuritis, pneumonia), neurological involvement which may lead to meningitis and encephalitis, gastrointestinal symptoms, in severe cases, acute colitis and pancreatitis can occur, and endocrine abnormalities may include thyroiditis and diabetes.

**Diagnosis can be very difficult** and it may also be difficult to determine the exact drug causing the hypersensitivity as first exposure may have started 8 weeks prior.
Common drugs causing DRESS include allopurinol, anti-epileptics, antibiotics, immunosuppresants, HIV treatment and NSAIDS. A careful drug history should be taken.

**The diagnosis should** be suspected when there is presence of the triad of extensive skin rash, high fever, and organ involvement, supported by a finding of eosinophilia and abnormal liver function tests.
RegiSCAR has proposed a diagnostic criteria and patients require at least 3 of the following:

- Hospitalisation
- Reaction suspected to be drug related
- Acute skin rash
- Fever about 38°C
- Enlarged lymph nodes at two sites
- Involvement of at least one internal organ
- Blood count abnormalities such as low platelets, raised eosinophils or abnormal lymphocyte count.

**Skin biopsy can help to confirm the diagnosis.**

- This may show inflammatory infiltrate in particularly eosinophils, extravasated erythrocytes and oedema.
- Regular blood tests including FBC, clotting, liver and renal function, CK, viral screen, glucose and thyroid function tests should be taken.
- **Investigations** looking for complications should be undertaken including ECG, CXR, echocardiogram, and urinalysis.

**DRESS syndrome treatment** requires all medications that are a possible culprits to be stopped and supportive care started.

- Antihistamines, topical steroids and emollients can be used to help control the rash.
- Careful fluid balance is necessary and clinicians should be aware of the patients nutritional status.
- Skin should be regularly checked and secondary infections should be treated with antibiotics.
- Systemic steroids may be started in severe cases where exfoliative dermatitis / pneumonitis / hepatitis is present.
- Occasionally immunosuppressants, intravenous immunoglobulin and plasmapheresis may be started.
- Potential culprit drugs should not be restarted again. The mortality is around 8%.

## Toxic epidermal necrolysis (TEN)

It is a potentially **life-threatening skin disorder** that is most commonly seen secondary to a **drug reaction**.
In which the skin develops a scalded appearance over an extensive area.
Some authors consider TEN to be the severe end of a spectrum of skin disorders which includes **erythema multiforme (EM)** and **Stevens-Johnson syndrome (SJS)**.

### Features:

- Systemically unwell e.g. pyrexia, tachycardia
- **Positive Nikolsky's sign**: the epidermis separates with mild lateral pressure.

### Drugs known to induce TEN:

- **Penicillins**
- **Sulphonamides**
- **Phenytoin**
- **Allopurinol**
- **Carbamazepine**
- **NSAIDs**

### Management:

- Stop precipitating factor.
- Supportive care, often in ICU.
- **IVIG** (Intravenous immunoglobulin) has been shown to be **effective** and is now commonly used **first-line.**
- Other treatment options include: Immunosuppressive agents (cyclosporine and cyclophosphamide), Plasmapharesis.

## Snake bite

- **Anti-venom** is most effective when given as early as possible, but it must be remembered that there is a **1%** chance of having an **anaphylactic reaction** to this, and so **adrenaline** should be available during its administration.
- Antivenom is given **IVI over 15 minutes**, and may be repeated after 12 hours if symptoms of systemic envenoming persist.
- The affected area should be immobilized **below** the level of the heart to minimize venous return.
- Any constricting **clothing** should be **removed**.

- Keep the victim **warm**, but **not** to give him warm drinks like caffeine and alcohol.
- **Ice** should **not** be used (as this has been associated with increased necrotic complications).
- Incisions/tourniquets should only be used by an **expert physician**.
- European viper venom antiserum is available and should be considered in the following situations:
  1) Persistent hypotension
  2) ECG abnormalities.
  3) Haemostatic abnormalities.
  4) **Marked local tissue swelling.**

## Hyperpyrexia

### Causes of Hyperpyrexia

- Salicylates
- Ecstasy
- Cocaine
- Neuroleptic malignant syndrome
- Serotonin syndrome
- Thyroid storm
- CO poisoning

## Fever in neutropenia

**Assessment of the febrile patient with neutropenia should include:**

- Assess for likely **sites** of infection from history, examination and CXR.
- Comprehensive **pan-cultures** of blood, urine, sputum, Hickman line (if present).
- **Barrier nursing** should be instituted if possible.
- If temperature more than 40°C for 4 to 6 hours or if the patient is hypotensive, **blind broad-spectrum antibiotic therapy** should be started (N.B. after taking cultures).
- Antibiotics **should be continued for 2 to 5 days after** the fever has settled and the neutrophil count has recovered.
- If **fever persists after 48 hours** despite antibiotic therapy, **fungal** (Aspergillus, Candida, Pneumocystis) or **viral** (CMV) infection should be considered.
- If infection with Staph aureus is suspected, the addition of **vancomycin** should be considered.

Although preferred antibiotic regimens for neutropenic fever vary from centre to centre, all operate on the same principles.
The aim is to provide **broad-spectrum coverage** that includes cover for **Pseudomonas** aeruginosa.

**Dual therapy regimes** are usually used: a broad-spectrum antibiotic (an antipseudomonal penicillin, carbapenem or ceftazidime) plus an anti-pseudomonal aminoglycoside. (EX: Tazocin + Gentamycin).

(**EX**: Tienam or Meronam or Tazocin **PLUS** Gentamicin or Amikacin ± Vancomycin ± Antifungal ± Anti-viral).

## Acute intermittent porphyria (AIP)

It is an **autosomal dominant** condition caused by a defect in **porphobilinogen deaminase**, an enzyme involved in the biosynthesis of haem.

It characteristically presents with **abdominal** and **neuropsychiatric** symptoms in **20-40 year olds**.

AIP is more common in **females** (5:1).

| Drugs which may precipitate attack: | Safe Drugs |
|---|---|
| 1) **Alcohol**<br>2) **Benzodiazepines**<br>3) **Barbiturates (Thiopentone)**<br>4) **Halothane**<br>5) **Oral contraceptive pill**<br>6) **Sulphonamides** | 1) Aspirin<br>2) Paracetamol<br>3) Codeine<br>4) Morphine<br>5) **Chlorpromazine**<br>6) Beta-blockers<br>7) Penicillin<br>8) Metformin |

A 43-year-old man presents with known acute intermittent porphyria is brought to the Emergency Department by the police due to an acute psychosis. What is the most suitable drug for sedation? >> **Chlorpromazine (NOT BDZs)**

# Clinical Sciences, Biostatistics & Miscellaneous

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# Biostatistics & EBM

## Statistical terms

The table below gives a brief definition of commonly encountered terms:

| Term | Description |
|---|---|
| Mean | The average of a series of observed values |
| Median | The middle value if series of observed values are placed in order |
| Mode | The value that occurs most frequently within a dataset |
| Range | The difference between the largest and smallest observed value |

## statistical terms used with screening tests and contingency table

The available data should be used to construct a contingency table as below:

**TP** = true positive; **FP** = false positive; **TN** = true negative; **FN** = false negative

| | Disease present | Disease absent |
|---|---|---|
| **Test positive** | **TP** | FP |
| **Test negative** | FN | **TN** |

The table below lists the main statistical terms used with screening tests:

| Measure | Formula | Plain English |
|---|---|---|
| **Sensitivity** | **TP / (TP + FN )** | Proportion of patients **with** the condition who have a **positive** test result. |
| **Specificity** | **TN / (TN + FP)** | Proportion of patients **without** the condition who have a **negative** test result. |

| | | |
|---|---|---|
| **Positive predictive value (PPV)** | **TP / (TP + FP)** | The chance that the patient **has** the condition if the diagnostic test is **positive** |
| **Negative predictive value (NPV)** | **TN / (TN + FN)** | The chance that the patient does **not** have the condition if the diagnostic test is **negative** |
| **Likelihood ratio for a positive test result** | **sensitivity / (1 - specificity)** | How much the odds of the disease increase when a test is positive |
| **Likelihood ratio for a negative test result** | **(1 - sensitivity) / specificity** | How much the odds of the disease decrease when a test is negative |

Positive and negative predictive values are prevalence dependent.
Likelihood ratios are not prevalence dependent.

**Increasing** the **cut-off** of a **positive** test result will **decrease** the number of **false positives** and hence increase the **specificity**.

**EX**: A new test to screen for pulmonary embolism (PE) is used in 100 patients who present to the Emergency Department. The test is positive in 30 of the 40 patients who are proven to have a PE. Of the remaining 60 patients, only 5 have a positive test. What is the sensitivity of the new test?

A contingency table can be constructed from the above data, as shown below:

| | PE diagnosed | NO PE |
|---|---|---|
| **Test positive** | 30 | 5 |
| **Test negative** | 10 | 55 |

The sensitivity = TP / (TP + FN)
The sensitivity is therefore 30 / (30 + 10) = 75%

**EX**: A new blood test is developed to screen for prostate cancer. Trials have shown it has a **sensitivity** for detecting clinically significant prostate cancer of **80%** but a **specificity** of **60%**.

What is the likelihood ratio for a positive test result?

Likelihood ratio for a positive test result = sensitivity / (1 - specificity)

= 0.8 / (1 - 0.6) = 2

# Graphical representation of data

| phase | goal | Notes |
|---|---|---|
| Animal trial | Safety for testing the drug in humans | |
| Phase I | • Initial safety<br>  ○ most frequent side effects<br>  ○ How the drug is metabolized and excreted. | • conducted in healthy volunteers.<br>• The number of subjects ranges from 20 to 80. |
| Phase II | Effectiveness<br>( RCTs) | The number of subjects ranges from a few dozen to about 300. |
| Phase III | Comparative efficacy<br>(Effectiveness compared to commonly used treatment) | • The number of subjects ranges from several hundred to about 3,000<br>• The best study for phase 3 is a randomised control study. |
| Phase IV (post marketing) | Side effects | Enrolls a large number of patients, typically several thousands. |

**Charts and diagrams**

| Quantitative data | Qualitative data |
|---|---|
| Histogram<br>Scatter diagram | Bar diagram<br>Pie diagram |

**The interpretation of novel findings in a published clinical research study**

- The trustworthiness of a study should depend solely on its scientific validity, that is, whether it is free of bias.
- **The conclusion should be treated with skepticism even if it is extensively peer-reviewed**

## When to do screening?: Wilson and Junger criteria

1. The condition should be **an important** public health problem.
2. There should be **an acceptable treatment for** patients with recognised disease.
3. **Facilities** for diagnosis and treatment should be available.
4. There should **be a recognised latent or early symptomatic stage.**
5. The natural **history** of the condition, including its development from latent to declared disease should be adequately understood.
6. There should be a suitable **test** or examination.
7. The test or examination should be **acceptable** to the population
8. There should be **agreed policy** on whom to treat.
9. The **cost** of case-finding (including diagnosis and subsequent treatment of patients) should be economically balanced in relation to the possible expenditure as a whole.
10. **Case-finding** should be a continuous process and not a 'once and for all' project.

**N.B: NOT** The condition should be potentially curable.

## Scales of measurement

Data always come in one of the four scales of measurement:

| | |
|---|---|
| Nominal | Data are divided into qualitative groups, such as hot/cold, with no implication of order. |
| Ordinal | Data are placed in an order (hot/hotter/hottest), although the absolute levels are unknown and no conclusion can be made about the size of the interval. |

| | |
|---|---|
| Interval | **dividing a continuous measurement into groups (eg age groups).**Data are placed in an order; and the exact value of the measurement is given, usually in measured quantities representing the difference between two measurements (81-90/91-100/101-110 °C). That is, differences between arbitrary pairs of measurements can be meaningfully compared. Ratios between numbers of the scale are not meaningful, so operations such as multiplication and division cannot be carried out directly. But ratios of differences can be expressed; for example, one difference can be twice Another If the measurement scale does not have an absolute zero (ie no numbers exist below the zero) this is called interval data. |
| Ratio | Here, there is a value of 0 kelvin, and it isn't possible to get below this (ie absolute zero), therefore, the ratio between the values is meaningful, eg 271-280/281-290/291-300 kelvin. |

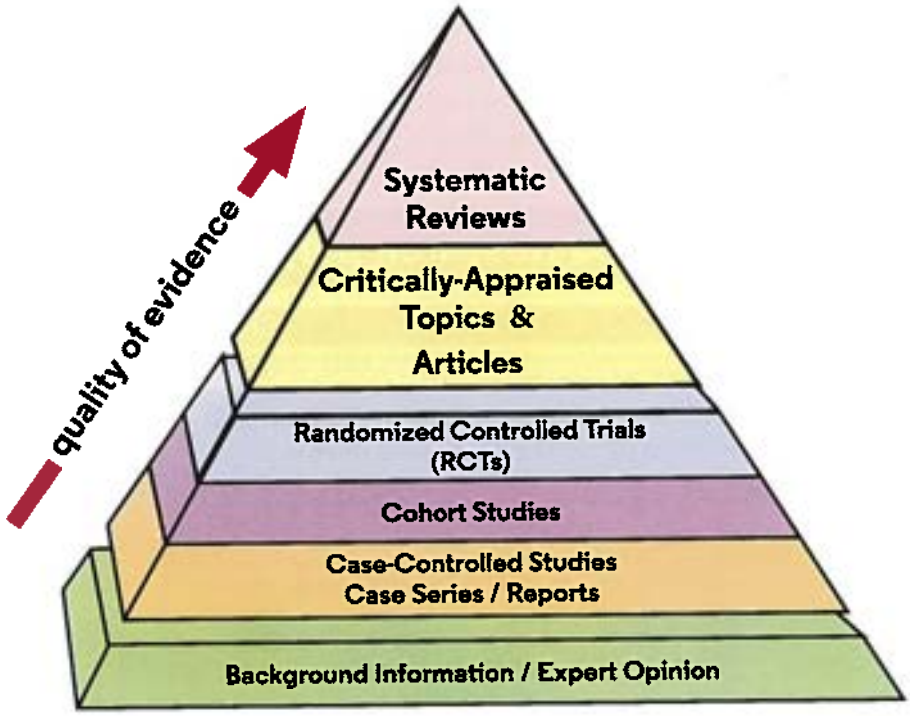
## Study Designs and Research purposes

| Objective | Study design |
|---|---|
| Describe of disease or spectrum | Case series or report<br>Cross sectional study |
| Determine operating characteristics of a new diagnostic test | Cross sectional study |
| Describe prognosis | Cohort study |
| Determine cause-effect | Cohort study<br>Case control study |
| Compare new interventions | Randomised clinical trial |
| summarize literature | Meta-analysis |

# Study design: evidence and recommendations

## Levels of evidence:

1) **Ia** - evidence from **meta-analysis** of **randomised controlled trials**
2) **Ib** - evidence from at least **one** randomised controlled **trial**
3) **IIa** - evidence from at least one well designed controlled trial which is not randomised
4) **IIb** - evidence from at least one well designed experimental trial
5) **III** - evidence from case, correlation and comparative studies
6) **IV** - evidence from a panel of **experts**




## Grading of recommendation:

- **Grade A** - based on evidence from at least one randomised controlled trial (i.e. Ia or Ib)
- **Grade B** - based on evidence from non-randomised controlled trials (i.e. IIa, IIb or III)
- **Grade C** - based on evidence from a panel of experts (i.e. IV)

## Sampling

- Sampling error arises when only a portion of the population is studied
- **Random sampling** implies that the sample has been selected from a sampling frame in such a way that every individual has the same chance of being selected
- **The standard error of the mean** is the standard deviation divided by the square root of the sample size, hence it must always be smaller than the standard deviation
- **Inference** is the process of drawing conclusions about the population using the sample information
- **a sample statistic is a point estimate of a population parameter**

## Intention to treat analysis

Intention to treat analysis is a method of analysis for randomized controlled trials (RCT) in which all patients randomly assigned to one of the treatments are analysed together, regardless of whether or not they completed or received that treatment.

Intention to treat analysis is done to **avoid** the effects of **crossover** and **drop-out**, which may affect the randomization to the treatment groups, so **include the patients who drop out in the final data set.**

In RCT >>> **include the patients who drop out in the final data set.**

## Study designs: main features

The following table highlights the main features of the main types of study:

| Study type | Key features |
|---|---|
| **Randomised controlled trial (RCT)** | Participants randomly allocated to intervention or control group (e.g. standard treatment or placebo). RCT is the gold standard for evaluation of efficacy for therapeutic and preventative measures.<br>Practical or ethical problems may limit use. |
| **Cohort study** | **Observational** and **prospective**.<br>Two (or more) are selected according to their exposure to a particular agent (e.g. medicine, toxin) and followed up to see how many develop a disease or other outcome.<br>The usual outcome measure is **relative risk (RR)**.<br>Examples include "**Framingham Heart Study**" |
| | **EX**: A cohort study is being designed to look at the relationship between **smoking** and **breast cancer**. The usual outcome measure in a cohort study is the **relative risk**. |
| **Case-control study** | Observational and **retrospective**.<br>Patients with a particular condition (cases) are identified and matched with (controls).<br>Data is then collected on past exposure to a possible causal agent for the condition.<br>The usual outcome measure is the **odds ratio**.<br>**Inexpensive**, produce **quick** results.<br>Useful for studying **rare conditions**.<br>Prone to confounding<br>EX: to assess whether living near electricity pylons is a risk factor for childhood leukaemia. |
| **Cross-sectional survey** | Provide a 'snapshot', sometimes called **prevalence** studies.<br>Provide **weak** evidence of cause and effect. |

A new antihypertensive drug needs to be investigated to establish its relative **potency**. Which of technique is most appropriate for this purpose >> **Bioassay** (Biological assays)
In a test of **efficacy** of an antihypertensive drug >> **a double blind, randomised** design would be favourable.

## Cohort study (more details)

In **cohort studies,** the study **sample is selected based on exposure to a risk factor.**
In **case-control studies**, the study **sample is selected according to having a disease or not**, and then it is determined which participants were exposed to a risk factor.

### Aim

- To study the incidence rate and whether a given exposure is associated with the outcome of interest

### Study method

- The researchers gather a group of study participants who have common characteristics.
- Participants are then classified into two groups: exposed and unexposed.
- The incidence of the outcome of interest is compared between the two groups.

### Advantages

- Less susceptible to recall bias than case-control studies.
- Helps determine whether a given exposure plays a role in the development of a disease
- Allows for the calculation of relative **risk**
- Helps determine **incidence**
- Can be used for **rare exposures**

### Disadvantages

- **When the outcome of interest is rare a very large sample size is needed (Insufficient for rare disease)**
- Prospective cohort studies are **high-cost** and **time-consuming**
- In retrospective cohort studies, some data on predictors and confounders may be missing because the data was collected in the past.
- Only assesses the exposures determined at the beginning of the study

## Types

| Types of cohort studies | | |
|---|---|---|
| | Prospective cohort study | Retrospective cohort study |
| **Description** | Study begins **before** the groups develop an outcome of interest | Study begins **after** the exposure and outcome of interest have already occurred |
| **Exposure** | Study participants are categorized into an exposed group and an unexposed group. | Study participants are categorized into a group that was previously exposed to a given risk factor (exposed; e.g., smoking) and a moup that was not (unexposed). |
| **Outcome** | The participants are **followed** prospectively for a **period of time** to see whether there is a difference in the rate at which the exposed and unexposed groups develop the outcome of interest. | Data previously collected about the participants is compared to see whether there was a difference in the rate at which the exposed and unexposed groups developed the outcome of interest (e.g., lung cancer) over a period of time. |
| **Example** | Individuals with a smoking history of 1 pack of cigarettes a day (exposed group) are compared to individuals who are non-smokers to see if there is a difference in the proportion of patients in each group that develop lung cancer (e.g., the outcome) within a specific follow-up period. | Individuals with a smoking history of 1 pack of cigarettes a day (exposed group) 5 years ago are compared to individuals who were non-smokers 5 years ago to see if there is a difference in the proportion of patients in each group that eventually develop |

# Observational study (more details)

## Disadvantages

- **From association in an observational study, we cannot infer cause and effect**

## Systematic review (meta-analysis)

- a study of studies.
- statistical (quantitative) combination of results from two or more studies addressing the same research question.
- Metanalysis= systematic reviews + Quantitative measures.
- Usually used to treatment studies.
- **A 'meta-analysis' would look at combining all previous data,. This is likely to be the quickest option to complete, and also produces the highest level of evidence.**
- **rapid and efficient**
- **Publication bias might be present** (positive results are published more often than the negative ones).
- Publication bias can be examined by funnel plots if a sufficient number of studies is found.
- Non-randomised or other studies may or may not be included.
- However, randomised controlled trials usually have lower risk of bias and hence give us more confidence about validity of results and are preferred primary sources for systematic review.
- Critical appraisal is an important part of systematic review and it has to be objectively performed using well-defined criteria or appraisal tools.
- Meta-analysis, that is, combining results numerically in a statistically appropriate way, though desirable, is not always feasible, depending on the availability of usable data and heterogeneity. **(Meta-analysis is not always performed)**
- The search strategy in systematic review should be comprehensive involving electronic databases and other sources and using well-defined search terms.
- **Case-control studies are not usually included in the search of literature in systematic review**
- The research question is always focused
- there are at least two authors to independently appraise the search results and primary studies.
- It is not mandatory to exclude studies with missing data.
- The effect size should not affect the weight of each study, although it will affect the final result.
- Trial quality is usually not incorporated into meta-analysis nowadays since the weightings can be subjective and arbitrary.

- **The weight of each study should depend on the sample size**
- **Funnel plots**
  - **show publication bias in meta-analyses**
- **Forest plot**
  - **The most appropriate way of graphically depicting the results of meta-analysis.**

**Fixed vs random effect model for meta-analysis**

| The fixed effect model | The random effects model |
|---|---|
| the most commonly used model for meta-analysis. **Provides the best estimate of the treatment effect** | |
| attempts to provide one single best estimate of treatment effect. | attempts to find an average treatment effect. |
| assumes there is no heterogeneity between the trials. | assumes heterogeneity |
| assumes a single treatment effect | allows multiple treatment effects. |

## Randomised controlled trial (RCT)

**Overview:** **The purpose of randomisation is to prevent systematic differences (bias) between treatment groups.**

**Aim:** to determine the possible effect of a specific intervention on a given population

### Advantages

- Minimizes bias
- Can demonstrate causality

### Disadvantages

- Cannot be used to evaluate **rare diseases**
  - For rare diseases and exposures, **case control studies are the best option.** Although cohort studies are good for rare exposures, they are not good for rare diseases.
- Cannot be used when treatments have well-known adverse side effects
- Expensive and time-consuming

### Uses

- the 'gold standard' for evaluating a new intervention
- May be used **to test an efficacy** of a drug

## Study method

- **Randomization:** Study participants are randomly allocated to either the treatmenUintervention group or the control group to ensure that both groups have approximately the same baseline characteristics.
- **Blinding:** the practice of not informing an individual or group about which study participants are part of the control group and which are part of the treatment group (used to reduce bias)
- **Classic errors in randomization**
  - Consecutive sampling, which may well not be representative if the study time is short.
  - Convenience sampling: strong potential for bias, with volunteers generally healthier than others.
  - Judgmental sample: including those that you want only. The potential for systematic error is enormous.

## Methods of analysis for randomized controlled trials

### Intention to treat analysis (ITT)

- Intention to treat analysis is a method of analysis for **randomized controlled trials** in which all patients randomly assigned to one of the treatments are analysed together, regardless of whether or not they completed or received that treatment.
  **Include the patients who drop out in the final data set**
- Intention to treat analysis is done to avoid the effects of crossover and drop-out, which may affect the randomization to the treatment groups.
- **ITT** helps to reduce bias by sticking to the original allocation of treatment and analysing the patient in that treatment group even if they do not receive the treatment
- **ITT** is considered to be the analysis which is least subject to bias.
  **Considered the most robust**

### Per protocol analysis

**A per protocol analysis** may exclude patients who suffered an event but then did not follow the protocol accurately, for example, a patient treated with the diabetes agent who was admitted to hospital, but missed one to two doses of medication

## Biological assays

**Biological assays** **are designed to measure the relative potency of different preparations.**

## Sequential trial

- a trial in which the data are analysed after each participant's results become available and the trial continues until a clear benefit is seen in one of the comparison groups, could also be used to assess efficacy, but there would have to be a large expected difference from placebo.
- 'Sequential' trial would be comparing one therapy to another sequentially (usually with wash out periods in between).

## Crossover trial

- The principle of a crossover design is that a patient has one drug or treatment, then a washout period, and then another drug, and the effect is compared between the two in a single individual.
- For this reason it is a good **study design for treatment of chronic conditions (eg: comparing analgesics in arthritis**) but not appropriate for acute conditions.

- **In a crossover trial, the patient (who usually has a chronic stable disease) receives one drug (or placebo) and then the other drug after a washout period**
- **Each patient will usually receive all drugs within the study**
- In this way, confounding can be greatly reduced
- If a drug had long-lasting effects it may not be easy to see which of the trial drugs was having an effect
- A self-limiting illness is difficult to study in this way
- Because each person is acting as their own control, it is usually possible to use smaller numbers to get the same power.
- **If any treatment in a cross-over trial is a disease-modifier (in the most extreme case, kills or cures the patient), then the interpretation of results in any subsequent period becomes impossible**. This is because disease modification implies that one course of the drug will permanently change the future timecourse of that patient's disease in some way, making a cross-over study un-interpretable. In this case a parallel trial is the only appropriate option.

# Study design: new drugs

When a new drug is launched there are a number of options available in terms of study design.

One option is a **placebo controlled trial**. Whilst this may provide robust evidence it may be considered **unethical** if established treatments are available and it also does **not provide a comparison with standard treatments**.

If a drug is therefore to be compared to an existing treatment a statistician will need to decide whether the trial is intended to show superiority, equivalence or non-inferiority:

- **Superiority**: whilst this may seem the natural aim of a trial one problem is the **large sample size needed** to show a significant benefit over an existing treatment.
- **Equivalence**: an **equivalence margin is defined (-delta to +delta)** on a specified outcome. If the confidence interval of the difference between the two drugs **lies within the equivalence margin** then the drugs may be assumed to have a similar effect.
- **Non-inferiority:** similar to equivalence trials, but only the lower confidence interval needs to lie within the equivalence margin (i.e. -delta). **Small sample sizes are needed** for these trials. Once a drug has been shown to be non-inferior large studies may be performed to show superiority.

It should be remembered that drug companies may not necessarily want to show superiority over an existing product. If it can be demonstrated that their product is equivalent or even non-inferior then they may compete on price or convenience.

**EX**: A new oral-hypoglycaemic is being developed. A number of different study types are considered to demonstrate efficacy in reducing the HbA1c. Which study designs would require the most patients to produce a significant result >>> **Superiority trial.**

# Significance tests

The type of significance test used depends on whether the data is **parametric** (something which can be **measured**, usually **normally distributed**) or non-parametric.

## Parametric tests:

- **Student's t-test** - **paired** or **unpaired**.
- **Pearson's product-moment coefficient** - **correlation**

## Non-parametric tests:

- **Mann-Whitney U test** - unpaired data.
- **Wilcoxon signed-rank test** - compares **two sets** of observations on a **single** sample.
- **Chi-squared test**: used to compare proportions or **percentages**.
- **Spearman, Kendall rank** – **correlation**.

**Paired** data refers to data obtained from **a single group of patients**, e.g. Measurement before and after an intervention.
**Unpaired** data comes from **two different groups** of patients, e.g. Comparing response to different interventions in two groups.

**To test Correlation**:

- **Parametric (normally distributed)>>> Pearson's coefficient.**
- **Non-parametric >>> Spearman's coefficient.**

**EX**: A study measures a patient's serum cholesterol before and after a new lipid-lowering therapy has been given. What type of significance test should be used to analyse the data? >>> **Student's paired t-test**.

**EX**: A study is designed to assess the efficacy of a new anti-hypertensive medication. **Two groups** of patients are **randomly** assigned, one to take the established drug for 3 months whilst the other takes the new drug for 3 months. Blood pressure is measured before and after the intervention. There is then a **period off medication** for 1 month. After this period has **elapsed the medication that the groups receive is swapped around** and again blood pressure is measured before and 3 months later. The difference in blood pressure after the respective medications is calculated for each patient. Which one of the significance tests is it most appropriate to apply?
This describes **a crossover study**. As we are comparing **parametric** data from the **same patients** (they swapped medication halfway through the study) the **Student's paired t-test** should be used.

A clinical trial is conducted to study the benefits of a new oral medication to improve the symptoms of patients with COPD. In the trial 300 patients with COPD are given the new medication and a further 300 COPD patients are given a placebo.
Three months later they are asked to rate their symptoms using the following scale: *much improved, slight improvement, no change, slight worsening, significantly worse*.
What is the most appropriate statistical test to see whether the new medication is beneficial? >>> **Mann-Whitney U test**

**EX**: A study is designed on 50 persons to look at the efficacy of a mandible advancement device in reducing snoring. The severity of snoring was assessed by the partner using a 10 point scale **before** and **after** using the device. >>> **Wilcoxon signed-rank test.**

- **Categorical variables are not continuous, e.g. drug/ placebo, dead/ alive. They should be described as percentages or proportions and compared with a Chi-squared test.**
- **Normally distributed continuous data should be described as mean and standard deviation and compared with a Student's t-test.**
- **Skewed continuous data should be described as median and range and compared using a test such as the Wilcoxon rank-sum test or the Mann-Whitney U-test**.

## Significance tests...Null hypothesis

A null hypothesis ($H_0$) states that two treatments are equally effective (and is hence negatively phrased).
A significance test uses the sample data to assess **how likely the null hypothesis is to be correct.**
**For example:**

- 'there is no difference in the prevalence of colorectal cancer in patients taking low-dose aspirin compared to those who are not'

The alternative hypothesis ($H_1$) is the opposite of the null hypothesis, i.e. there is a difference between the two treatments.

The **p value** is **the probability of obtaining a result by chance at least as extreme** as the one that was actually observed, **assuming that the null hypothesis is true.** It is therefore equal to the chance of making a type I error (see below).

## Two types of errors may occur when testing the null hypothesis:

- **Type I:** the **null hypothesis is rejected when it is true** - i.e. Showing a difference between two groups when it doesn't exist, a false positive. This is determined against a preset significance level (termed alpha). As the significance level is determined in advance the chance of making a type I error is not affected by sample size. It is however increased if the number of end-points are increased. For example if a study has 20 end-points it is likely one of these will be reached, just by chance.
- **Type II:** the **null hypothesis is accepted when it is false** - i.e. failing to spot a difference when one really exists, a false negative. The probability of making a type II error is termed beta. It is determined by both sample size and alpha.

| | Study accepts $H_0$ | Study rejects $H_0$ |
|---|---|---|
| **Reality $H_0$** | | Type 1 error (alpha) |
| **Reality $H_1$** | Type 2 error (beta) | Power (1 - beta) |

The **power of a study** is the probability of (correctly) **rejecting the null hypothesis when it is false**, i.e. the probability of detecting a statistically significant difference.

- **Power = 1 - the probability of making a type II error.**
- Power can be increased by **increasing the sample size.**

## The power of a study may be defined in a number of ways:

- In general terms, the probability that a **statistically significant difference** will be detected.
- Probability of (correctly) **rejecting** the **null hypothesis** when it is **false**.
- Which also means the probability of **confirming** the **alternative hypothesis** when **the alternative hypothesis is true.**
- **Power = 1 - the probability of a type II error** or **1 – β.**

The significance level of a test is defined as the probability of rejecting the null hypothesis when the null hypothesis is actually true (a Type I error). It is often represented by the Greek symbol alpha.

A study is only statistically significant if the p-value reaches the significance level set before the study is started. Popular levels of significance are **5% (0.05)**, **1% (0.01)** and **0.1% (0.001).**

# Choosing the appropriate test

Choosing of a test to examine a statistical problem depends upon the scale of measurement (nominal, ordinal, interval, ratio) and the type of question being asked
a non-parametric test would give less power

## Student's t- test

### Paired *t* test

- Compares a **single measure** (variable) recorded **on a single group** of individuals **on two different occasions.**
- Is used to compare **means in a single sample, for example, before and after treatment**.
- >> comparing **means** (not proportions) in the **same subjects**
- **paired *t*-test is used to compare post-treatment and pre-treatment result of a single group.**
- eg: the same subject measured before and after a process change, or the same subject measured at different times.
- As both sets of measurements were made on the same patients, the measurements are not independent

### unpaired t-test (independent sample *t*-test)

- is the most appropriate statistical test to compare means of two independent samples.
  - compare the **means of two** different populations
- An independent sample *t*-test may be used in a study of **two independent** treatment groups, and the **sample sizes are relatively large** (>30 in each group) and the variable is **Normally distributed**.
- eg: Blood pressure is a continuous variable which is normally distributed; as such Student's *t* test is the most appropriate way to test for **differences in the mean BPs between the two groups.**
- For example, suppose we are evaluating the effect of a medical treatment, and we enroll 100 subjects into our study, then randomly assign 50 subjects to the treatment group and 50 subjects to the control group. In this case, we have two independent samples and would use the unpaired form of the *t*-test.
- eg: 2 groups (treatment group & placebo group) In a randomised controlled trial of drug A for treatment of hypercholesterolemia

## Log-rank test

- **Is the most appropriate test to compare two survival curves with censored data.**
- Log-rank test should be used to compare survival data between two groups, but not compare median survival. Mean survival is not known unless all patients have died.
- If a question presented survival data and some observations are censored (ex: not came for follow up) and the outcomes are not known. We need to use survival analysis for such data and the log-rank test is the appropriate test to use **to compare survivals in two independent groups**.
- **can be used to test the difference in relapse rate between the two groups**

## McNemar's test

- is applied to binary data, but is only applicable to paired data, used to compare proportions
- McNemar's test is used to compare paired samples - either case control studies where each case is matched to a control, or to studies where two treatments are given to matched subjects.
- It cannot be used where the sample size differs.
- is used to test for agreement of repeated observations.

## Regression techniques

- are used to predict the value of one variable based on the other
- **Multiple regression**
  - is used to analyse the relationship between one dependent variable and one or more independent variables
- **Logistic regression** (**Log regression analysis**)
  - It is used to describe the relationship between one dependent binary variable and one or more metric independent variables.
  - It is commonly used to assess plasma concentrations of a drug as it allows examination of the relationship between possible confounding factors such as renal function or age.
  - This would allow us to determine whether one variable is dependent on another, ex: in case whether drug concentration was dependent on body surface area.
    - **ANOVA (analysis of variance)** is an example of logistic regression analysis.
      - ➢ is a statistical test which tests for co-variance between populations and is useful when variables such as age, sex

or race may be expected to affect the treatment's effectiveness.

- tests for a difference in mean values between a **number of groups**
- **Is the most appropriate to compare the means of more than two groups. (used for more than two means)**
- **One-way analysis of variance** is identical mathematically to the unpaired Student t-test when just two groups are being compared.
- **The one-way (analysis of variance) (ANOVA)** compares the means of the **groups**
- The means should be presented with confidence intervals to give the reader an idea of whether the differences between the groups were significant

## Normal distribution

The normal distribution is also known as the **Gaussian distribution** or **'bell-shaped' distribution.**
The Normal distribution **is a continuous** probability distribution.
It describes the spread of many biological and clinical measurements.

- **Symmetrical** i.e. **Mean = Mode = Median**
- **68.3% of values lie within 1 SD of the mean.**
- **95.4% of values lie within 2 SD of the mean.**
- **99.7% of values lie within 3 SD of the mean.**
- This is often reversed, so that within 1.96 SD of the mean lie 95% of the sample values
- The range of the mean - (1.96 *SD) to the mean + (1.96 * SD) is called the 95% confidence interval, i.e. If a repeat sample of 100 observations are taken from the same group 95 of them would be expected to lie in that range

### Standard deviation (SD):

- The SD is a **measure** of **how much dispersion** exists from the **mean.**
- SD = square root (variance)
- **If SD increased the power of study is reduced .**
- **The standard deviation would give the best estimate of a spread of a measurement about the mean**
- Variance is the square of standard deviation. Standard deviation is the square root of variance.

For normally distributed data **95.4% of values lie within 2** standard deviations of the mean, **leaving 4.6% outside** this range. Therefore **2.3%** of values will be higher and **2.3%** will be lower than 2 standard deviations from the mean. This figure is sometimes approximated to 2.5%

## Confidence interval and standard error of the mean (SEM)

The confidence interval is a common and sometimes misunderstood principle in medical statistics.

- A formal definition may be: a range of values for a variable of interest constructed so that this range has a specified probability of including the true value of the variable. The specified probability is called the confidence level, and the end points of the confidence interval are called the confidence limits.
- In simpler terms: **a range of values within** which **the true effect** of **intervention** is likely to lie.

The likelihood of the true effect lying within the confidence interval is determined by the confidence level.

For example a confidence interval at the 95% confidence level means that the confidence interval should contain the true effect of intervention 95% of the time.

### How is the confidence interval calculated?

The standard error of the mean (SEM) is a measure of the spread expected for the mean of the observations - i.e. how 'accurate' the calculated sample mean is from the true population mean.

### Key point:

**SEM = SD / square root (n)**

- (**SEM**) is Standard error of the mean.
- **SD** = standard deviation
- and **n** = sample size (number of patients)
- Therefore the SEM gets smaller as the sample size (n) increases.

**EX**: A small study looks at the weight of patients diagnosed with type 2 DM. Overall 64 patients were reviewed. The average weight was 81 kg, with a standard deviation of 12 kg.

The standard error of the mean= 12 / square root (64) = 12 / 8 = 1.5

**A 95% confidence interval:**

- lower limit = mean - (1.96 * SEM)
- upper limit = mean + (1.96 * SEM)

**The above formula is a slight simplification:**

- If a small sample size is used (e.g. n < 100) then it is important to use a 'Student's T critical value' look-up table to replace 1.96 with a different value.
- If a different confidence level is required, e.g. 90% then 1.96 is replaced by a different value. For 90% this would 1.645.

## Skewed distributions

**Normal** (Gaussian) distributions: mean = median = mode.
**Positively** skewed distribution: mean > median > mode.
**Negatively** skewed distribution mean < median < mode.

To remember the above note how they are **in alphabetical order**, think positive going forward with '>', whilst negative going backwards '<'

## Confounding

In statistics confounding refers to a variable which correlates with other variables within a study leading to spurious results.

### For example

- a case-control study looks at whether low-dose aspirin can prevent colorectal cancer
- the proportion of people diagnosed with colorectal who took aspirin is compared to the proportion of people without colorectal cancer who took aspirin
- if the case and control groups are not matched for age then age could be said to be a confounding factor as older people are more likely to take aspirin and also more likely to develop cancer

In another example a study which finds that people who drink coffee are more likely to develop heart disease. The confounding factor in this study is smoking. Smoking is associated with both drinking coffee and heart disease. People who drink coffee are also more likely to smoke. In this case smoking confounds the apparent relationship between coffee and heart disease.

Confounding occurs when there is a non random distribution of risk factors in the populations. Age, sex and social class are common causes of confounding.

In the design stage of an experiment, confounding can be controlled by randomisation which aims to produce an even amount of potential risk factors in two populations.

In the analysis stage of an experiment, confounding can be controlled for by stratification.

## Correlation and linear regression

Two measurements, or variables, may be plotted on a scatter plot.

For example, a study is performed to assess the correlation between age and systolic blood pressure. Age may be marked along the x axis and systolic blood pressure along the y axis.

### Correlation:

The **correlation coefficient** (sometimes referred to as **Pearson's product-moment coefficient**) indicates how closely the points lie to a line drawn through the plotted data.

It is denoted by the **value r** which may lie **anywhere between -1 and 1.**

**For example:**

- **r = 1 - strong positive** correlation (e.g. systolic blood pressure always increases with age).
- **r = 0 - no** correlation (e.g. there is no correlation between systolic blood pressure and age).
- **r = - 1 - strong negative** correlation (e.g. systolic blood pressure always decreases with age).

Whilst correlation coefficients give information about how one variable may increase or decrease as another variable increases they **do not give information about how much the variable will change**.

They also **do not provide** information on **cause** and **effect**.

It **can't be** used to **predict** systolic blood pressure for a given age.

## Linear regression:

In contrast to the correlation coefficient, linear regression may be used to **predict how much one variable changes when a second variable is changed**.

A regression equation may be formed, $y = a + bx$, where

- y = the variable being calculated
- a = the intercept value, when x = 0
- b = the slope of the line or regression coefficient. Simply put, how much y changes for a given change in x
- x = the second variable

# Odds and odds ratio

**Odds** are a ratio of the **number of people who incur a particular outcome** to **the number of people who do not incur the outcome**.

The **odds ratio** may be defined as the ratio of the odds of a particular outcome with experimental treatment and that of control.

**Odds** - remember a ratio of the number of people who **incur** a particular outcome to the number of people who **do not incur** the outcome. **NOT** a ratio of the number of people who **incur** a particular outcome to the **total** number of people.

## Odds vs. probability:

In contrast, probability is the fraction of times you'd expect to see an event in many trials.

When expressed as a single number probability is always between 0 and 1. So, if we take the example of rolling a dice:

- The probability of rolling a six is 1/6 or 0.166666
- The odds of rolling a six is 1/5 or 0.2

**Odds ratios** are the usual reported measure in **case-control** studies.
It **approximates** to **relative risk if the outcome of interest is rare**.

For example, if we look at a trial comparing the use of paracetamol for dysmenorrhoea compared to placebo we may get the following results:

| | Total number of patients | Achieved = 50% pain relief |
|---|---|---|
| **Paracetamol** | **60** | **40** |
| **Placebo** | **90** | **30** |

The **odds** of achieving significant pain **relief** with **paracetamol** = 40 / 20 = 2.

The **odds** of achieving significant pain **relief** with **placebo** = 30 / 60 = 0.5.

Therefore the **odds ratio** = 2 / 0.5 = 4

**EX**: A study looks at whether golf actually increases the risk of medial epicondylitis. Sixty people who regularly play golf are matched to sixty people who do not play golf. Thirty of the golfers had developed medial epicondylitis at some point compared to ten of the non-golfers.
**What is the odds** ratio of developing medial epicondylitis for people who play golf?
**Odds** of a golfer developing medial epicondylitis = 30 / 30 = 1.
**Odds** a non-golfer developing medial epicondylitis = 10 / 50 = 0.2.
The **odds ratio** is therefore = 1 / 0.2 = 5.

## Relative risk (RR)

**Relative risk (RR)** is the ratio of risk in the experimental group (experimental event rate, EER) to risk in the control group (control event rate, CER).

The term relative risk ratio is sometimes used instead of relative risk.

It is the usual outcome measure of **cohort** studies.

### To recap:

- EER = rate at which events occur in the experimental group
- CER = rate at which events occur in the control group

For example, if we look at a trial comparing the use of paracetamol for dysmenorrhoea compared to placebo we may get the following results:

| | Total number of patients | Experienced significant pain relief |
|---|---|---|
| **Paracetamol** | **100** | **60** |
| **Placebo** | **80** | **20** |

**Experimental event rate, EER** = 60 / 100 = 0.6
**Control event rate, CER** = 20 / 80 = 0.25
Therefore the **relative risk ratio** = **EER / CER** = 0.6 / 0.25 = 2.4

**If the risk ratio is > 1** then the rate of an event (in this case experiencing significant pain relief) is increased compared to controls.

It is therefore appropriate to calculate the **relative risk increase (RRI)** if necessary (see below).

**If the risk ratio is < 1** then the rate of an event is decreased compared to controls. The **relative risk reduction (RRR)** should therefore be calculated (see below).

**Relative risk increase (RRI)** or **Relative risk reduction (RRR)** is calculated by **dividing** the **absolute risk** change by the **control** event rate.
Using the above data, RRI = (EER - CER) / **CER** = (0.6 - 0.25) / 0.25 = 1.4 = 140%

**Remember that risk and odds are different:**
If 20 patients die out of every 100 who have a myocardial infarction then the **risk** of dying is 20 / 100 = 0.2 whereas the **odds** are 20 / 80 = 0.25.

## Numbers needed to treat (NNT) and absolute risk reduction (ARR)

Numbers needed to treat (NNT) is a measure that indicates **how many patients** would require an intervention to reduce the expected number of outcomes by **one**.

**EX:** Results demonstrate that number needed to treat (**NNT**) is **20** for the prevention of the primary end-point.
This prevention study for stroke reveals that **20 patients need to be treated to prevent one event.**
Thus if you treat a **1000** patients then you will expect to have **50** fewer strokes.

It is calculated by **1/ (Absolute risk reduction)** and is rounded to the next highest whole number.

**NNT = 1 / Absolute Risk Reduction (ARR)**

**Experimental event rate (EER)** = (Number who had particular outcome with the intervention) / (**Total** number who had the intervention).
**Control event rate (CER)** = (Number who had particular outcome with the control/ (**Total** number who had the control).

**Absolute risk reduction (ARR) = CER-EER or EER-CER?**

The absolute risk reduction (ARR) may be calculated by finding the absolute difference between the control event rate (CER) and the experimental event rate (EER).

You will often find both versions of the above listed in different sources.

In some ways in doesn't matter which you use as you will end up with the same answer but from a technical point of view:

- If the outcome of the study is **undesirable** then ARR = CER - EER
- If the outcome of the study is **desirable** then ARR* = EER - CER

*This may be more accurately termed absolute benefit increase, rather than absolute risk reduction

**EX**: A study is carried out to assess the potential of hip protectors to reduce femoral neck fractures in elderly nursing home patients. The average age of the patients was 82 years. Over a two-year period 800 patients were recruited and assigned randomly either to the hip protector group or standard care group.
**The results:**
Hip protector group: **400** patients - **10** of whom had a femoral neck fracture over the two year period.
Control group: **400** patients - **20** of whom had a femoral neck fracture over the two year period.
What is the absolute risk reduction?
**The absolute risk reduction (ARR) = CER-EER, where:**
**CER** = 20 / 400 = 1 / 20 = 0.05
**EER** = 10 / 400 = 1 / 40 = 0.025
**ARR** = CER - EER = 0.05 - 0.025 = 0.025

**EX**: A study is designed to assess a new proton pump inhibitor (PPI) in elderly patients who are taking aspirin. The new PPI is given to 120 patients whilst a control group of 240 is given the standard PPI. Over a five year period 24 of the group receiving the new PPI had an upper GI bleed compared to 60 who received the standard PPI. What is the absolute risk reduction?

Absolute risk reduction = (Control event rate) - (Experimental event rate).
(ARR) = CER-EER
Control event rate = 60 / 240 = 0.25
Experimental event rate = 24 / 120 = 0.2

Absolute risk reduction = 0.25 - 0.2 = 0.05 = 5% reduction

**EX**: A new drug is trialled for the treatment of lung cancer. Drug A is given to **500** people with early stage non-small cell lung cancer and a placebo is given to **450** people with the same condition. After 5 years **300** people who received drug A had survived compared to **225** who received the placebo.

What is the number needed to treat to save one life?
The question asks about the number needed to treat to **save one life**. The 'event' is therefore **survival**.

Experimental (drug A) event rate (**EER**) = 300 / 500 = 0.6
Control (placebo) event rate (**CER**) = 225 / 450 = 0.5

Absolute risk reduction (**ARR**) = 0.6 - 0.5 = 0.1
Number needed to treat (**NNT**) = 1 / 0.1 = 10

**EX**: A study looks at the benefits of adding a new antiplatelet drug to aspirin following a myocardial infarction. The following results are obtained:

Percentage of patients having further MI within 3 months was **4%** of patients treated with aspirin only, while was **3%** with patients treated with aspirin + the new drug.
What is the number needed to treat to prevent one patient having a further myocardial infarction within 3 months?
NNT = 1 / Absolute Risk Reduction.
NNT = 1 / (control event rate - experimental event rate).
= 1 / (0.04-0.03) = 1 / (0.01) = 100

**EX**: A **randomised controlled trial** is performed to look at a new drug to prevent hip fractures in postmenopausal women. Group A consists of 1,000 women who take the new drug whilst group B contains 1,400 women taking a placebo. The hip fracture rate in group A is 2% and in group B is 4%.

What is the number needed to treat to prevent one hip fracture?
They key to answering this question is to ignore irrelevant data such as the number of patients in each group.
Control event rate (**CER**) = 4% = 0.04
Experimental event rate (**EER**) = 2% = 0.02
Absolute risk reduction (**ARR**) = 0.04 - 0.02 = 0.02

**NNT** = 1 / Absolute Risk Reduction.
Number needed to treat (NNT) = 1 / 0.02 = 50.

## Hazard ratio (HR)

The hazard ratio (HR) is **similar to relative risk** but is used when risk is not constant to time. It is typically used when **analysing survival over time.**

**EX:** A study is performed comparing **two chemotherapy regimens** for patients with small cell lung cancer. The end point of the study is **survival time.**

## Incidence and prevalence

These two terms are used to describe the **frequency** of a condition in a population.

**The incidence** is the number of **new** cases per population in a given time **period.**

For example, if condition X has caused 40 new cases over the past 12 months per 1,000 of the population the annual incidence is 0.04 or 4%.

**The prevalence** is the **total** number of cases per population at **a particular point in time.**

For example, imagine a questionnaire is sent to 2,500 adults asking them how much they weigh. If from this sample population of 500 of the adults were obese then the prevalence of obesity would be 0.2 or 20%.

### Relationship:

- **Prevalence = incidence * duration of condition**
- In **chronic** diseases the **prevalence** is much greater than the incidence
- In **acute** diseases **the prevalence and incidence are similar**. For conditions such as the common cold the incidence may be greater than the prevalence.

## Pre- and post- test odds and probability

### Pre-test probability:

The proportion of people with the target disorder in the population at risk at a specific time (point **prevalence**) or time interval (period **prevalence**).

For example, the prevalence of rheumatoid arthritis in the UK is 1%

### Post-test probability:

The proportion of patients with that particular test result who have the target disorder

Post-test probability = post-test odds / (1 + post-test odds)

### Pre-test old

The odds that the patient has the target disorder before the test is carried out

Pre-test odds = pre-test probability / (1 - pre-test probability)

### Post-test odds

The odds that the patient has the target disorder after the test is carried out

Post-test odds = pre-test odds x likelihood ratio

where the likelihood ratio for a positive test result = sensitivity / (1 - specificity)

## Funnel plot

A funnel plot is primarily used to demonstrate the **existence** of **publication bias** in **meta-analyses.**

**Funnel plots >>> show publication bias in meta-analyses**

Funnel plots are usually drawn with treatment effects on the horizontal axis and study size on the vertical axis.

### Interpretation:

- A symmetrical, inverted funnel shape indicates that publication bias is unlikely.
- Conversely, an asymmetrical funnel indicates a relationship between treatment effect and study size. This indicates either publication bias or a systematic difference between smaller and larger studies ('small study effects').

# Bias

Bias describes the situation in a trial where one outcome is systematically favored. It should be noted that there is considerable variation in the definitions and classification of bias.

The table below lists some of the more common types of bias.

| Type | Description |
|---|---|
| **Selection bias** | **Error in assigning individuals to groups leading to differences which may influence the outcome.**<br>Subtypes include **sampling bias** where the subjects are not representative of the population. This may be due to **volunteer bias**. An example of volunteer bias would be a study looking at the prevalence of *Chlamydia* in the student population. Students who are at risk of *Chlamydia* may be more, or less, likely to participate in the study. A similar concept is **non-responder bias**. If a survey on dietary habits was sent out in the post to random households it is likely that the people who didn't respond would have poorer diets than those who did.<br><br>**Other examples include**<br>• loss to follow up bias<br>• prevalence/incidence bias (Neyman bias): when a study is investigating a condition that is characterised by early fatalities or silent cases. It results from missed cases being omitted from calculations<br>• admission bias (Berkson's bias): cases and controls in a hospital case control study are systematically different from one another because the combination of exposure to risk and occurrence of disease increases the likelihood of being admitted to the hospital<br>• healthy worker effect |

| Type | Description |
|---|---|
| **Recall bias** | Difference in the accuracy of the recollections retrieved by study participants, possibly due to whether they have disorder or not. E.g. a patient with lung cancer may search their memories more thoroughly for a history of asbestos exposure than someone in the control group. A particular problem in **case-control studies.** |
| **Publication bias** | Failure to publish results from valid studies, often as they showed a negative or uninteresting result. Important in meta-analyses where studies showing negative results may be excluded. |
| **Work-up bias (verification bias)** | In studies which compare new diagnostic tests with gold standard tests, work-up bias can be an issue. Sometimes clinicians may be reluctant to order the gold standard test unless the new test is positive, as the gold standard test may be invasive (e.g. tissue biopsy). This approach can seriously distort the results of a study, and alter values such as specificity and sensitivity. Sometimes work-up bias cannot be avoided, in these cases it must be adjusted for by the researchers. |
| **Expectation bias (Pygmalion effect)** | Only a problem in non-blinded trials. Observers may subconsciously measure or report data in a way that favours the expected study outcome. |
| **Hawthorne effect** | **Describes a group changing it's behaviour due to the knowledge that it is being studied** |
| **Late-look bias** | Gathering information at an inappropriate time e.g. studying a fatal disease many years later when some of the patients may have died already |
| **Procedure bias** | Occurs when subjects in different groups receive different treatment |
| **Lead-time bias** | **Occurs when two tests for a disease are compared, the new test diagnoses the disease earlier, but there is no effect on the outcome of the disease** |

# THE CELL

## Cell organelles

The table below summarises the main functions of the major cell organelles:

| Organelle/macromolecule | Main function |
|---|---|
| Endoplasmic reticulum | **Rough endoplasmic reticulum:**<br>• translation and folding of new proteins<br>• manufacture of lysosomal enzymes<br>• site of N-linked glycosylation<br>• examples of cells with extensive RER include pancreatic cells, goblet cells, plasma cells<br>**Smooth endoplasmic reticulum:**<br>• steroid, **lipid synthesis**<br>• examples of cells with extensive SER include those of the adrenal cortex, hepatocytes, testes, ovaries |
| Golgi apparatus | Modifies, sorts, and packages these molecules that are destined for cell secretion<br>Site of O-linked glycosylation |
| **Mitochondrion** | Aerobic respiration. Contains mitochondrial genome as **double-stranded circular DNA** |
| Nucleus | DNA maintenance and RNA transcription |
| **Lysosome** | Breakdown of **large** molecules such as **proteins** (**peptides**) and polysaccharides |
| Nucleolus | Ribosome production |
| **Ribosome** | **Translation** of **RNA into proteins** |
| **Peroxisome** | Catabolism of **very long chain fatty acids and amino acids**<br>Results in the formation of hydrogen peroxide ($H_2O_2$) |
| **Proteasome** | Along with the lysosome pathway involved in **degradation** of **protein** molecules that have been tagged with ubiquitin |

## Cell cycle

The cell cycle is regulated by proteins called cyclins which in turn control cyclin-dependent kinase (CDK) enzymes

| Phase | Notes | Regulatory proteins |
|---|---|---|
| $G_0$ | • 'resting' phase<br>• quiescent cells such as hepatocytes and more permanently resting cells such as neurons | |
| $G_1$ | • **G**ap 1, cells increase in size<br>• **determines length of cell cycle**<br>• under influence of p53 | Cyclin D / CDK4, Cyclin D / CDK6 and Cyclin E / CDK2: regulates transition from G1 to S phase |
| **S** | • **S**ynthesis of DNA, RNA and histone<br>• centrosome duplication | Cyclin A / CDK2: active in S phase |
| $G_2$ | • **G**ap 2, cells continue to increase in size | Cyclin B / CDK1: regulates transition from $G_2$ to M phase |
| **M** | • **M**itosis - cell division<br>• the shortest phase of the cell cycle | |

## Microtubules

Microtubules are components of the cytoskeleton of the cytoplasm. They help **guide movement during intracellular transport and also help bind internal organelles.** Microtubules are found in all cells except red blood cells.

### Structure

- cylindrical structure composed of alternating α and β tubulin subunits which polymerize to form protofilaments
- microtubules are polarized, having a positive and negative end

### Molecular transport

- attachment proteins called dynein and kinesin move up and down the microtubules facilitating the movement of various organelles around the cell
- dynein moves in a retrograde fashion, down the the microtubule towards the centre of the cell (+ve → -ve)
- kinesin moves in an anterograde fashion, up the microtubule away from the centre, towards the periphery (-ve → +ve)

# Cell division

There are two types of cell division; mitosis and meiosis.

**The table below demonstrates the key differences:**

| Mitosis | Meiosis |
|---|---|
| Occurs in **somatic** cells | Occurs in **gametes** |
| Results in **2 diploid** daughter cells | Results in **4 haploid** daughter cells |
| Daughter cells are genetically **identical** to parent cell | Daughter cells contain one homologue of each chromosome pair and are therefore genetically **different** |

## Remember:

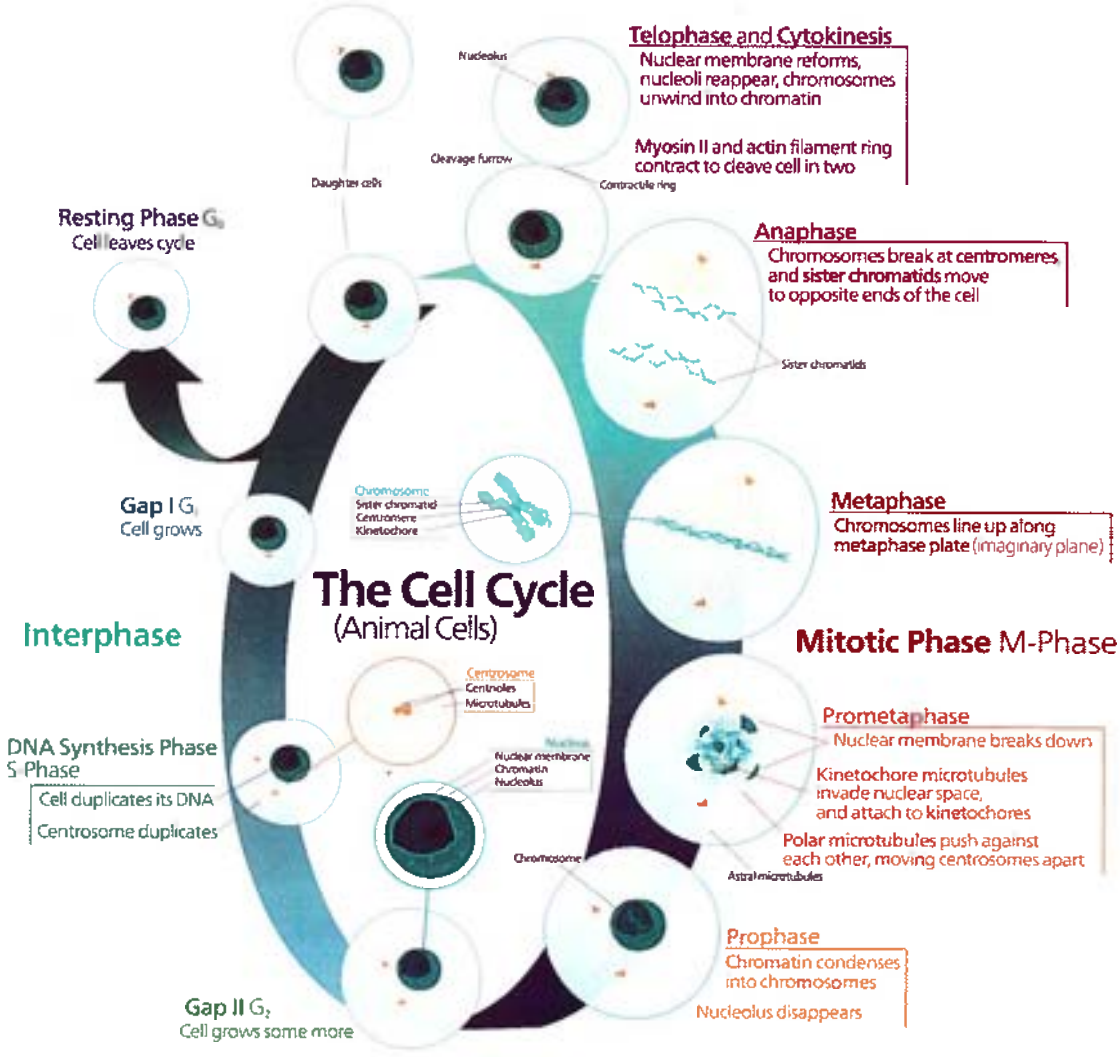
- Somatic cells have 22 pairs of autosomes and 1 pair of sex chromosomes, i.e. 46XY or 46XX.
- Cells with a normal chromosome complement are known as **diploid** cells.
- Gametes (ova or spermatozoa) have a single copy of each chromosome and are known as **haploid** cells.

## Mitosis

Mitosis occurs during the **M** phase of the cell cycle.
It describes the process in which somatic cells divide and replicate producing genetically identical diploid daughter cells.
This allows tissue to grow and renew itself.
During the S phase of the cell cycle the cell prepares itself for division by duplicating the chromosomes.

**The table below shows the phases of mitosis itself:**

| Prophase | Chromatin in the nucleus condenses |
|---|---|
| **Prometaphase** | Nuclear membrane breaks down allowing the microtubules to attach to the chromosomes |
| **Metaphase** | Chromosomes aligned at **m**iddle of cell |
| **Anaphase** | The paired chromosomes separate at the kinetochores and move to opposite sides of the cell |
| **Telophase** | Chromatids arrive at opposite poles of cell |
| **Cytokinesis** | Actin-myosin complex in the centre of the cell contacts resulting in it being 'pinched' into two daughter cells |


Telophase and Cytokinesis
Nuclear membrane reforms, nucleoli reappear, chromosomes unwind into chromatin
Myosin II and actin filament ring contract to cleave cell in two
Nucleolus
Cleavage furrow
Daughter cells
Contractile ring
Resting Phase G0
Cell leaves cycle
Anaphase
Chromosomes break at centromeres and sister chromatids move to opposite ends of the cell
Sister chromatids
Gap I G1
Cell grows
Chromosome
Sister chromatid
Centromere
Kinetochore
Metaphase
Chromosomes line up along metaphase plate (imaginary plane)
The Cell Cycle
(Animal Cells)
Interphase
Mitotic Phase M-Phase
Centrosome
Centrioles
Microtubules
Prometaphase
Nuclear membrane breaks down
DNA Synthesis Phase
S Phase
Cell duplicates its DNA
Centrosome duplicates
Nucleus
Nuclear membrane
Chromatin
Nucleolus
Kinetochore microtubules invade nuclear space, and attach to kinetochores
Polar microtubules push against each other, moving centrosomes apart
Chromosome
Astral microtubules
Prophase
Chromatin condenses into chromosomes
Nucleolus disappears
Gap II G2
Cell grows some more

# Cell surface proteins

The table below shows the most common cell surface proteins associated with particular cell types:

| Type of cell | Cell surface markers |
|---|---|
| Haematopoietic stem cells | CD34 |
| Helper T cell | CD4, TCR, CD3, CD28 |
| Cytotoxic T cell | CD8, TCR, CD3, CD28 |
| Regulatory T cell | CD4, CD25, TCR, CD3, CD28 |
| B cell | CD19, CD20, CD40, MHC II, B7 |
| Macrophage | CD14, CD40, MHC II, B7 |
| Natural killer cell | CD16, CD56 |

The table below lists the major clusters of differentiation (CD) molecules and describes their function.

| Cluster of differentiation | Function |
|---|---|
| **CD1** | MHC molecule that presents lipid molecules |
| **CD2** | Found on thymocytes, T cells, and some natural killer cells that acts as a ligand for CD58 and CD59 and is involved in signal transduction and cell adhesion |
| **CD3** | The signalling component of the T cell receptor (TCR) complex |
| **CD4** | Found on helper T cells.<br>Co-receptor for **MHC class II**<br>**Used by HIV to enter T cells** |
| **CD5** | Found in the majority of mantle cell lymphomas |
| **CD8** | Found on cytotoxic T cells.<br>**Co-receptor for MHC class I**<br>Found on a subset of myeloid dendritic cells |
| **CD14** | Cell surface marker for macrophages |
| **CD15** | Expressed on Reed-Sternberg cells (along with CD30) |
| **CD16** | Bind to the Fc portion of IgG antibodies |
| **CD21** | **Receptor for Epstein-Barr virus** |
| **CD28** | Interacts with B7 on antigen presenting cell as costimulation signal |
| **CD45** | Protein tyrosine phosphatase present on all leucocytes |
| **CD56** | Unique marker for natural killer cells |
| **CD95** | Acts as the FAS receptor, involved in apoptosis |

GP41 play a role in the initial step for HIV entry into cells

**Gp120 fuses to the CD4 receptor, this then allows GP41 to penetrate the cell membrane**

- CD4+ CD25+ Fox-P3 + T regulatory cells are thought to be the most important T regulatory cell population. They are thought to play an important role in regulating immune responses after invading organisms have been tackled and preventing the development of autoimmunity.
- Regulatory T cells are **not** thought to produce IL-2.
- A small population of CD8+ human regulatory T cells has been identified in addition to the larger population of CD4+ regulatory cells.
- All T cells express the CD3 receptor, and in humans only 5-10% of CD4+ cells are regulatory T cells.

## Puberty

**Failure of menarche by age 16** is a recognised sign of **delayed puberty** and should prompt targeted examination and appropriate investigations.

Both hypogonadotrophic causes such as low weight / malnutrition, and hypergonadotrophic causes such as Turner's syndrome are recognised.

### Recognised signs of delayed puberty in girls include:

- **Menarche has not occurred by age 16.**
- **Absence** of **pubic hair** by age **14**
- **Absence** of **breast** development by age **14** years
- More than 5 years between the start and completion of breast growth

### Recognised signs of delayed puberty in boys include:

- **No testicular** enlargement by age **14** years
- **Absence** of **pubic hair** by age **15**
- More than 5 years between the start and completion of growth of the genitalia.

# Menstrual cycle

The menstrual cycle may be divided into the following phases:

| | Days |
|---|---|
| **Menstruation** | 1- 4 |
| **Follicular phase (proliferative phase)** | 5 -13 |
| **Ovulation** | 14 |
| **Luteal phase (secretory phase)** | 15 - 28 |

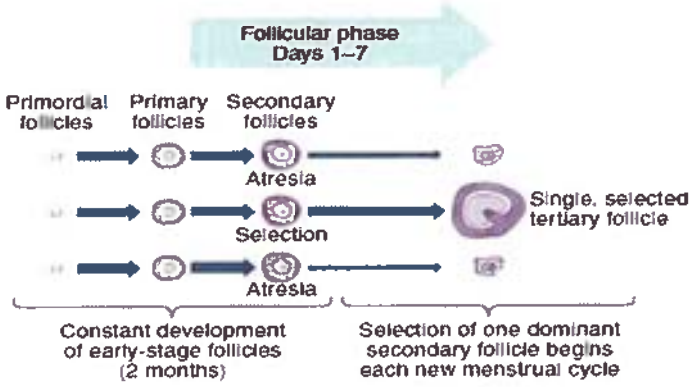
| | Follicular phase (proliferative phase) (from day 1 until day 14) | Luteal phase (secretory phase) (From day 15 until day 28) |
|---|---|---|
| **Ovarian histology** | • A number of follicles develop.<br>• One follicle will become dominant around the mid-follicular phase | Corpus luteum |
| **Endometrial histology** | Proliferation of endometrium | Endometrium changes to secretory lining under influence of progesterone |
| **Hormones** | • A rise in FSH results in the development of follicles which in turn secrete oestradiol<br>• When the egg has matured, it secretes enough oestradiol to trigger the **acute release of LH. This in turn leads to ovulation**<br>• **Graafian follicle** is a large mature tertiary follicle containing an oocyte that is ready to be ovulated.<br>• Ovulation occurs 14 days before menses, regardless of cycle length.<br>• estradiol stimulates the growth of the **endometrium**.<br>• Progesterone levels are **low**<br>• **FSH activates aromatase within granulosa cells, increasing estradiol production.**<br>• The main hormone controlling the follicular phase is **estradiol**, secreted by **Granulosa cells.** | Progesterone secreted by corpus luteum rises through the luteal phase.<br><br>If fertilisation does not occur the corpus luteum will degenerate and progesterone levels fall<br><br>Oestradiol levels also rise again during the luteal phase |

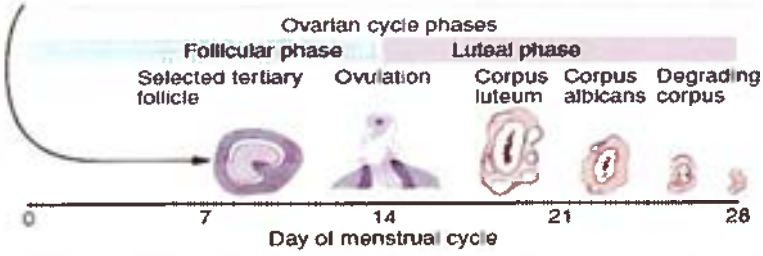
| | Follicular phase (proliferative phase) (from day 1 until day 14) | Luteal phase (secretory phase) (From day 15 until day 28) |
|---|---|---|
| **Cervical mucus** | • Following menstruation the mucus is thick and forms a plug across the external os<br>• Just prior to ovulation the mucus becomes clear, acellular, low viscosity. It also becomes 'stretchy' - a quality termed spinnbarkeit | Under the influence of progesterone it becomes thick, scant, and tacky |
| **Basal body temperature** | Falls prior to ovulation due to the influence of oestradiol | **Rises** following ovulation in response to higher progesterone levels |

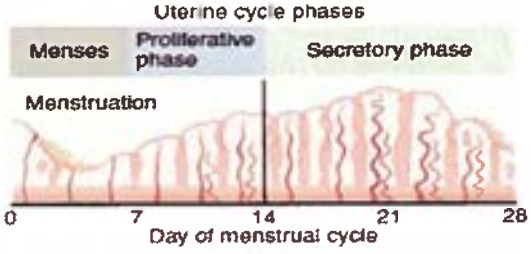
**Which hormone levels would be most likely to indicate the occurrence of ovulation?** **>> Luteinising hormone**

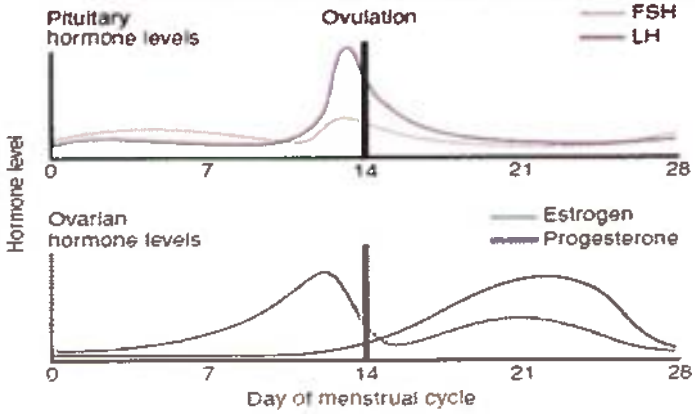
**At which point in the menstrual cycle do progesterone levels peak?**
**>> Luteal phase**
- Progesterone is secreted by the corpus luteum following ovulation.

**Which mechanism is most likely responsible for the missed period in early pregnancy?** **>> Syncytiotrophoblast produces human chorionic gonadotropin (hCG), which stimulates progesterone production by the corpus luteum.**


Follicular phase
Days 1–7
Primordial follicles
Primary follicles
Secondary follicles
Atresia
Selection
Single, selected tertiary follicle
Atresia
Constant development of early-stage follicles (2 months)
Selection of one dominant secondary follicle begins each new menstrual cycle


Ovarian cycle phases
Follicular phase
Luteal phase
Selected tertiary follicle
Ovulation
Corpus luteum
Corpus albicans
Degrading corpus
0
7
14
21
28
Day of menstrual cycle


Uterine cycle phases
Menses
Proliferative phase
Secretory phase
Menstruation
0
7
14
21
28
Day of menstrual cycle


Pituitary hormone levels
Ovulation
FSH
LH
Hormone level
0
7
14
21
28
Ovarian hormone levels
Estrogen
Progesterone
0
7
14
21
28
Day of menstrual cycle

# Thymus

***T cells** = **Thymus***
***B cells** = **Bone marrow***

The Thymus arises from the Third pharyngeal pouch

**Embryology:** Thymus epithelium arises from the 3rd pharyngeal pouch (endoderm).

**Function:** **Maturation and differentiation of T lymphocytes**

**Location**

- The thymus is a gland composed of two identical lobes, located in the superior anterior superior mediastinum, in front of the heart and behind the sternum.

**Clinical significance**

- Thymic hypoplasia or aplasia: DiGeorge syndrome, SCID
- Thymoma: tumor of thymic epithelial cells: Seen in myasthenia gravis, pure red cell aplasia, immunodeficiency with thymoma

**Thymic cortex and medulla**

- The **cortex** is the area of the thymus that is dense and full of immature T cells.
- The **medulla** is the area of the Thymus that is **pale** and full of **mature T cells**

# Lymphocytes

- T and B lymphocytes express receptors on their surface that recognise antigen in a specific manner. Each individual lymphocyte expresses a single type of receptor with unique specificity (except dual specificity T cells - see below).
- The receptor on the B lymphocyte is membrane bound immunoglobulin (IgM and IgD isotype) and recognises particulate antigen, whilst the T cell receptors TCR is a heterodimer that recognises peptide fragments presented by MHC molecules.
- The antigen specificity of T and B cells is generated during development by recombination of gene segments encoding the variable domains (antigen recognition domains) of immune receptors.

## B cells (B lymphocytes)

**Origin:** Originate and mature in the bone marrow

### Function

- Major component of the adaptive immune system: The humoral immune response of the adaptive immune system mainly consists of B cells and antibodies.
- After activation, B cells differentiate into plasma cells that produce and secrete antibodies

### Surface proteins

- B cells express numerous proteins on their surface:
  - **CD19, CD20, CD21 (used by EBV), and CD40**
  - **MHCII**
  - **IgG**
  - **B7**

### Plasma cells

- Plasma cells are fully differentiated cells from B-cells and hence lack these features (i.e. they lack surface-bound IgG and MHC class II and cannot undergo somatic hypermutation or isotype switching).
- plasma cells do not have surface-bound IgG (unlike B-cells).
- plasma cells cannot undergo somatic hypermutation (unlike B-cells).
- plasma cells cannot undergo isotype switching (unlike 8-cells).

## T cells (T lymphocytes)

**Origin:** Originate from lymphoid progenitor cells in the bone marrow and mature in the thymus.

### Distribution

- **T lymphocytes compose the majority of circulating lymphocytes in plasma.**
- **Lymph nodes:**
  - **The paracortical areas** contain T cells and accessory cells.
  - B cells are found within the cortex in follicles, which have central areas known as germinal centres.
  - **The medulla** contains large blood vessels and sinuses, and medullary cords that contain plasma cells secreting antibody.

## Function

- A major component of the adaptive immune response
- Essential for cell-mediated immunity
  - T lymphocytes are involved in cell-mediated acquired immune responses, whereas B lymphocytes are involved in humeral immunity and produce immunoglobulins.

## Mechanism of action

- T cells recognise antigen only when presented by (self) MHC molecules on an antigen presenting cell **(Co-operation with other cell types is required for T cell recognition of antigen)**
- **Patients with HIV have a deficiency of T-cells** (CD4 T-cell lymphocytes)

## T cell subtypes

- T cells are largely divided into cytotoxic T cells (CDS+), T helper cells (CD4+), and regulatory T cells.

What is the predominant site in the lymph node that contains T cells?
**>> Paracortex**

CDS proteins on the surface of cytotoxic T cells interact with MHC I receptors, while CD4 proteins on the surface of T-helper cells interact with MHC II receptors.

**Rule of 8: - MHC I x CD 8 = 8. - MHC II x CD 4 = 8.**

## T-Helper cells

**There are two major subsets of T-Helper cells:**

**Th1:**

- Involved in the **cell mediated response** and **delayed (type IV) hypersensitivity.**
- Secrete **IFN-gamma, IL-2, and IL-3.**

**Th2:**

- Involved in mediating **humoral (antibody) immunity.**
- e.g. stimulating production of IgE in asthma
- Secrete **IL-4, IL-5, IL-6, IL-10, IL-13**

**MRCP part 1 exam: What is most commonly secreted agent by T-helper cells subset 2 (Th2 cells)?**
**>>** Interleukin 4

**B lymphocytes VS T lymphocytes**

| | B lymphocytes | T lymphocytes |
|---|---|---|
| **Site of production** | **bone marrow.** germinal centre of lymph nodes and spleen. | produced in the bone marrow butmature in the **thymus** Paracortical region of lymph nodes and spleen. |
| **Functions** | **Humoral immunity**<br>• antibody production (immunoglobulins)<br>• control of pyogenic bacteria prevention of blood-borne infections.<br>• neutralization of toxins. | **Cell-mediated immunity;**<br>• protection against intracellular organisms, protozoa and fungi;<br>• graft rejection;<br>• control of neoplasms. |
| **% of total lymphocytes** | • 12%<br>• mainly fixed. | 70-80% (the majority of circulating lymphocytes in plasma).<br>• **mainly circulating;**<br>• long-lived memory cells. |

## Human genome

The human genome is stored on **23 chromosome pairs**.

The **haploid** human genome has a total of **3 billion DNA base pairs**, making up an estimated **20,000-25,000 protein-coding genes.**

**Human genome >>** 25,000 protein-coding genes

# HLA associations

HLA antigens are encoded for by **genes** on **chromosome 6**.

HLA A, B and C are class I antigens whilst DP, DQ, DR are class II antigens.

Questions are often based around which diseases have strong HLA associations. The most important associations are listed below:

## HLA-A3:

- Haemochromatosis

## HLA-B5:

- Behcet's disease

## HLA-B27:

- Ankylosing spondylitis
- Reiter's syndrome
- Acute anterior uveitis

## HLA-DQ2/DQ8:

- Coeliac disease

## HLA-DR2:

- Narcolepsy
- Goodpasture's

## HLA-DR3:

- Dermatitis herpetiformis
- Sjogren's syndrome
- Primary biliary cirrhosis

## HLA-DR4:

- Type 1 diabetes mellitus*
- Rheumatoid arthritis - in particular the **DRB1 gene** (DRB1*04:01 and DRB1*04:04 hence the association with DR4)

| | | |
|---|---|---|
| **HLA A3:** Haemochromatosis | **HLA-B5**: Behcet's disease | |
| | **HLA-B27:**<br>1. Ankylosing spondylitis<br>2. Reiter's syndrome<br>3. Acute anterior uveitis | |
| | **HLA-B35:** Subacute thyroiditis | |
| | **HLA-DQ2/DQ8:**<br>• Coeliac disease | **HLA-DR2:**<br>1. Narcolepsy.<br>2. Goodpasture's. |
| | | **HLA-DR3:**<br>1) Primary biliary cirrhosis (also **DR8**).<br>2) Sjogren's syndrome.<br>3) Dermatitis herpetiformis. |
| | | **HLA-DR4:**<br>• DM T1<br>• RA |

**NB**: DM T1 is associated with HLA-DR3 but is more strongly associated with HLA-DR4.

**NB**: Around **70%** of patients with **rheumatoid arthritis** are **HLA-DR4**. Patients with **Felty's syndrome** (a **triad** of rheumatoid arthritis, splenomegaly and neutropenia) are even more strongly associated with **90%** being **HLA-DR4**.

**MHC I-associated loci (HLA-A/-B/-C) only have 1 letter after the hyphen, while MHC II- associated loci (HLA- DR/- DP/- DQ) have 2 letters.**

**MRCP part 1exam: Which HLA subtypes is usually implicated with respect to matching for avoiding hyperacute rejection?**

**>> HLA-C**

- Anti-HLA-C IgG antibodies are usually implicated in hyperacute rejection; specifically,
- HLA-CW5 subtype antibodies have been implicated most in hyperacute rejection ofrenal transplant.

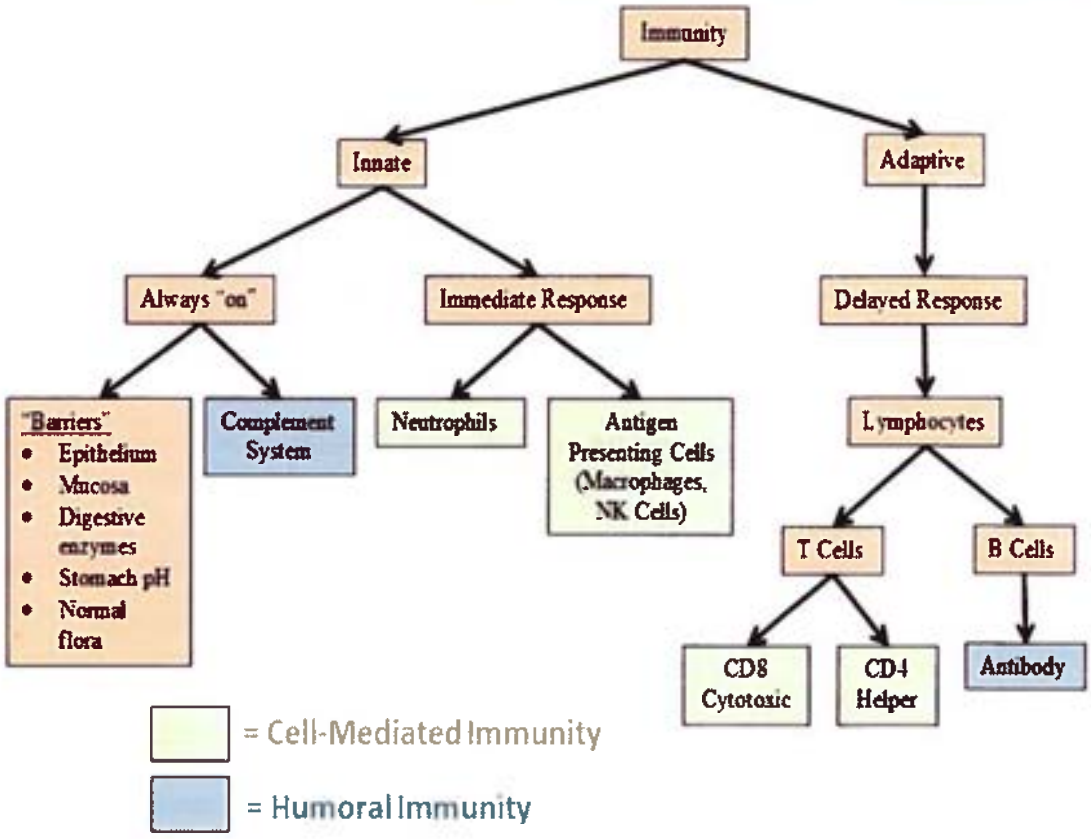
# Immune system cells: innate immune response

The following cells are mostly involved in the innate immune response:

| Cell type | Functions and properties |
|---|---|
| **Neutrophil** | Primary phagocytic cell in acute inflammation<br>Granules contain myeloperoxidase and lysozyme<br>Most common type of white blood cell<br>Multi-lobed nucleus |
| **Basophil** | Releases histamine during allergic response<br>Granules contain **histamine** and **heparin**<br>Expresses IgE receptors on the cell surface<br>Bi-lobed nucleus |
| **Mast cell** | Present in tissues and are similar in function to basophils but derived from different cell lines<br>Granules contain **histamine** and **heparin**<br>Expresses IgE receptors on the cell surface |
| **Eosinophil** | Defends against protozoan and helminthic infections<br>Bi-lobed nucleus |
| **Monocyte** | Diffferentiates into macrophages<br>Kidney shaped nucleus |
| **Macrophage** | Involved in **phagocytosis** of cellular debris and pathogens.<br>Acts as an antigen presenting cell (**APC**).<br>Major source of **IL-1**.<br>**Foam cells** are **fat-laden macrophages.** |
| **Natural killer cell (NK)** | Induce **apoptosis** in virally infected and tumour cells |
| **Dendritic cell** | Acts as an antigen presenting cell (APC) |

## Innate VS Adaptive immune response

| Innate (non-specific system) | Adaptive (acquired system) |
|---|---|
| **Components**<br>➢ Anatomical and physiological barriers<br>➢ Inflammatory response with leakage of antibacterial serum proteins (acute-phase proteins) and phagocytic cells<br>➢ Phagocytosis by neutrophils and macrophages<br>➢ Com lement s stem | **Components**<br>➢ Cell-mediated response effected by T cells<br>➢ Humeral immune response effected by B cells |
| **Properties**<br>➢ Rapid: responds within minutes to infection<br>➢ No antigenic specificity, i.e. the same molecules and cells respond to range of pathogens<br>➢ No memory, i.e. the response does not change after repeated exposure<br>➢ Preformed or rapidly formed components | **Properties**<br>➢ Slow: response over days to weeks<br>➢ Antigenic specificity i.e. each cell is a programmed genetically to respond to a single antigen<br>➢ Immunological memory, i.e. on repeated the response is faster, stronger and qualitatively different<br>➢ Diversity: ability to recognize and respond to a vast number of different antigens<br>➢ Self/non-self-recognition: i.e. lack of response (tolerance) to self-antigens but response to foreign<br>➢ antig ens |




# Macrophages

## Overview

- Macrophages are a type of antigen-presenting cell, defined as a lymphocyte that is able to phagocytose debris, toxins, cells or pathogens.
- **Origin:** Monocytes migrate to tissue and differentiate into macrophages.
- **Activated by** γ-interferon.
- Has a long life in tissues, which differentiates it from a circulating blood monocyte
- **Important cellular component of granulomas** (eg, TB, sarcoidosis), where they may fuse to form giant cells.

## Tissue-specific subtypes

- Osteoclasts (bone)
- Kupffer cells {liver)
- Microglia {brain and spinal cord)
- Histiocytes (connective tissue)

A patient undergoes liver biopsy, which shows t phagocytes with kidney-shaped nuclei. What are these cells called?
>> Kupffer cells (the names of macrophaqes can differ in each tissue)

What signaling molecule activates macrophages? **>> γ-interferon**

## Important macrophage forms in various Diseases

- Lipid laden macrophage (Foam cells) = **Hyperlipidemia & Atherosclerotic plaques.**
- Hemosiderin laden macrophage (Heart failure cells) = **CHF.**
- Macrophages containing debris from ingested Lymphocytes (Tingible body macrophage) = **Benign reactive lymphadenitis.**
- Macrophages containing PAS +ve, gram +ve rod shaped bacilli within Lamina propria in small intestine = **Whipple Disease.**
- Iron trapped in Macrophages in Bone marrow= Anemia of chronic disease.
- Macrophages containing Carbon pigment along pleural lymphatics = **Anthracosis.**
- Tissue paper like macrophage = **Gaucher disease.**

**The lipid A component of bacterial lipopolysaccharide (LPS) binds to CD14 on macrophages, which can trigger septic shock**

# Pathogenesis of atherosclerosis

- Chronic stress on the endothelium
- Endothelial dysfunction, which leads to
  - Invasion of inflammatory cells (mainly monocytes and lymphocytes) through the disrupted endothelial barrier
  - Adhesion of platelets to the damaged vessel wall >> platelets release inflammatory mediators (e.g., cytokines) and platelet-derived growth factor (PDGF)

  - PDGF stimulates migration and proliferation of smooth muscle cells (SMC) in the tunica intima and mediates differentiation of fibroblasts into myofibroblasts
- Inflammation of the vessel wall
- Macrophages and SMCs ingest cholesterol from oxidized LDL and transform into foam cells.
- Foam cells accumulate to form fatty streaks (early atherosclerotic lesions).
- Lipid-laden macrophages and SMCs produce extracellular matrix (e.g., collagen) >> development of a fibrous plaque (atheroma)
- Inflammatory cells in the atheroma (e.g., macrophages) secrete matrix metalloproteinases >> weakening of the fibrous cap of the plaque due to the breakdown of extracellular matrix >> minor stress ruptures the fibrous cap
- Calcification of the intima (the amount and pattern of calcification affect the risk of complications)
- Plaque rupture >> exposure of thrombogenic material (e.g., collagen) >> thrombus formation with vascular occlusion or spreading of thrombogenic material

### Foam cells

- **Foam cells** are a feature of atherosclerotic plaques and **are essentially lipid-laden macrophages.**
- They may also be seen as a reaction to:
  - silicone leakage around breast implants, and
  - inhaled organic antigens.

**MRCPUK exam: You are examining tissue biopsied from around a leaking silicone breast implant. It is rich in foam cells. What is the cell lineage of foam cells? >> Macrophage**

## Fibroblasts

- **The most common cell** type in connective tissue
- **Origin:** derived from mesenchymal stem cells
- Found in the interstitial spaces of organs.
- **Histological features: spindle-shaped cells** arranged in a branching pattern

- **Function:**
  - synthesis and organization of the extracellular matrix (ECM) and collagen
  - plays a critical role in wound healing
  - play a critical role in an immune response to a tissue injury.
  - They are **early players in initiating inflammation** in the presence of invading microorganisms. Tissue damage stimulates fibrocytes and induces the mitosis of fibroblasts.
  - **Responsible for forming the cap over an atherosclerotic plaque.**
- **Pathologic fibrosis** is characterized by uncontrolled fibroblast activation that results in exaggerated and persistent ECM accumulation and remodeling.

## Granulomatous inflammation

### Definition

- A pattern of chronic inflammation. Can be induced by persistent T-cell response to certain infections (eg, TB), immune-mediated diseases, and foreign bodies.
- A granuloma is a collection of macrophages: giant cells as a nidus of chronic inflammation

**Mechanism:** **Macrophages** >> jcytokine secretion (eg, TNF) >> formation of epithelioid macrophages and giant cells

### Types of granuloma and causes

#### Caseating granulomas

- Granulomas with central necrosis
- Found in **infections** e.g., tuberculosis, fungal infections, **tertiary syphilis**, *Bartonella henselae* (cat scratch disease)

#### Noncaseating granulomatous inflammation

- Granulomas without central necrosis
- Found in **immune-mediated diseases** (e.g., sarcoidosis, Crohn disease), sarcoidosis, vasculitis, and foreign body exposure

**TNF-a is important for maintaining the granuloma. It is essential to test patients for latent TB before initiating anti-TNF therapy because the drug causes breakdown of the granuloma and can result in disseminated TB.**

# Primary immunodeficiency

Primary immunodeficiency disorders may be classified according to which component of the immune system they affect.

## Neutrophil disorders:

| Disorder | Underlying defect | Notes |
|---|---|---|
| **Chronic granulomatous disease** | Lack of NADPH oxidase reduces ability of phagocytes to produce reactive oxygen species | Causes recurrent pneumonias and abscesses, particularly due to catalase-positive bacteria (e.g. Staphylococcus aureus and fungi (e.g. Aspergillus) |
| **Chediak-Higashi syndrome** | Microtubule polymerization defect which leads to a decrease in phagocytosis | Affected children have 'partial albinism' and peripheral neuropathy. Recurrent bacterial infections are seen |
| **Leukocyte adhesion deficiency** | Defect of LFA-1 integrin (CD18) protein on neutrophils | Recurrent bacterial infections. Delay in umbilical cord sloughing may be seen |

## B-cell disorders:

| Disorder | Underlying defect | Notes |
|---|---|---|
| **Common variable immunodeficiency** (CVID) | Many varying causes | Hypogammaglobulinaemia is seen.<br>May predispose to:<br>1) Recurrent chest infection >>> **TTT**: **IVIG**.<br>2) Autoimmune disorders.<br>3) Lymphoma.<br>4) Predisposition to malignancy. |

| | | |
|---|---|---|
| **Bruton's congenital agammaglobulinaemia** | Defect in Bruton's tyrosine kinase (BTK) gene that leads to a severe block in B cell development | X-linked recessive. Recurrent bacterial infections are seen |
| **Selective immunoglobulin A deficiency** | Maturation defect in B cells | • **Most common primary antibody deficiency.**<br>• Recurrent sinus and respiratory infections<br>• Associated with coeliac disease and may cause false negative coeliac antibody screen |

## T-cell disorders:

| Disorder | Underlying defect | Notes |
|---|---|---|
| **DiGeorge syndrome** | 22q11.2 **deletion**, failure to develop 3rd and 4th pharyngeal pouches | Common features include congenital heart disease, learning difficulties, **hypocalcaemia** (dt: parathyroid gland hypoplasia), thymus hypoplasia, recurrent **viral/fungal** diseases. |

## Combined B- and T-cell disorders:

| Disorder | Underlying defect | Notes |
|---|---|---|
| **Severe combined immunodeficiency (SCID)** | Many varying causes. Most common (X-linked) due to defect in the common gamma chain, a protein used in the receptors for IL-2 and other interleukins. Other causes include **adenosine deaminase deficiency** | **Recurrent infections due to viruses, bacteria and fungi. Stem cell transplantation may be successful** |

| | | |
|---|---|---|
| **Ataxia telangiectasia** | Defect in DNA repair enzymes | Autosomal recessive. Features include cerebellar ataxia, telangiectasia, recurrent chest infections and 10% risk of developing malignancy, lymphoma or leukaemia |
| **Wiskott-Aldrich syndrome (WAS)** | Defect in **WASP gene** | **X-linked recessive**. Features include **(4):**<br>• Recurrent bacterial infections (Chest)+<br>• Eczema+<br>• Low PLT+<br>• Low IgM levels.<br>At ↑ risk of lymphoreticular malignancy. |

1 ry Immunodeficiency dt **Combined** B- and T-cell disorders are >>> **SCID+ WAS+ Ataxic** (SCID, Wiskott-Aldrich syndrome, ataxic telangiectasia).

**EX**: Male pt. 20 years old has **recurrent oesophageal candidiasis**, also has asthma on steroids, eczema, No B cells, **Low Igs, low PLT, normal CD count (so NOT HIV)** >>> **Primary** immunodeficiency (**Wiskott-Aldrich Syndrome**).

# Cytokines

## Interleukin 1 (IL-1)

- It is a key mediator of the immune response.
- It is **secreted mainly by macrophages and monocytes** and acts as a **costimulator** of **T** cell and **B** cell proliferation.
- Other effects include increasing the expression of adhesion molecules on the endothelium. By stimulating the release by the endothelium of **vasoactive** factors such as PAF, nitric oxide and prostacyclin it also causes **vasodilation** and increases vascular permeability.
- It is therefore one of the **mediators of shock in sepsis**.
- Along with IL-6 and TNF, it acts on the **hypothalamus** causing **pyrexia**.

### IL-1 inhibitors are increasingly used in medicine.

### Examples include:

**anakinra**

- IL-1 receptor antagonist
- used in the management of rheumatoid arthritis

**canakinumab**

- monoclonal antibody targeted at IL-1 beta
- used systemic juvenile idiopathic arthritis and adult-onset Still's disease

## Interleukin-2 (IL-2)

**Produced by** Th1 cells (mainly CD4+ cells)

### Functions

- Stimulates proliferation and differentiation of T cells (helper, cytotoxic, regulatory T cells, and natural killer cells)
- Activates macrophages
- IL-2 is part of the body's natural response to microbial infection, and in discriminating between foreign ("non-self") and "self".
- there is some evidence that IL-2 may be involved in itchy psoriasis

### Therapeutic use

- **High-dose interleukin-2 can produce a high rate of response and durable remissions in patients with metastatic renal cancer.**
- IL-2 analog (aldesleukin): metastatic melanoma and renal cell carcinoma
- IL-2 antagonists (e.g., basiliximab): prevention of renal transplant rejection

## Tumour necrosis factor (TNF)

### Overview

- Tumour necrosis factor **(TNF) is a pro-inflammatory cytokine** with multiple roles in the immune system
- TNF is secreted mainly by macrophages
- act mainly in a paracrine fashion

### Function

- Activates macrophages and neutrophils, acts as co-stimulator for T cell activation
- Increased acute phase proteins
- Similar properties to IL-1 , induced pyrexia
- **TNF is important in the pathogenesis of rheumatoid arthritis.**
  - TNF blockers (e.g. infliximab, etanercept) are now licensed for treatment of severe rheumatoid
- A key cytokine in the pathogenesis of multi-organ failure , a Key mediator of bodies response to Gram negative septicaemia. **High concentrations of TNF induce shock-like symptoms**
- Exerts an interferon-like effect against viruses
- Enhanced HLA class I expression
- Anti-tumour effect (e.g. phospholipase activation)
- TNF-alpha binds to both the p55 and p75 receptor. These receptors can induce apoptosis. It also cause activation of NFkB
- Endothelial effects include increase expression of selectins and increased production of platelet activating factor, IL-1 and prostaglandins
- Promotes the proliferation of fibroblasts and their production of protease and collagenase.

- the prolonged exposure to **low concentrations of TNF can result in cachexia**, a wasting syndrome. This can be found, for example, in cancer patients.
- **Raised levels lead to increased insulin resistance**

## TNF blockers

**Used to treat IBD, rheumatoid arthritis, ankylosing spondylitis and psoriasis.**

**Examples**

- infliximab: monoclonal antibody, IV administration
- Etanercept: fusion protein that mimics the inhibitory effects of naturally occurring soluble TNF receptors, subcutaneous administration
- adalimumab: monoclonal antibody, subcutaneous administration

**Adverse effects of TNF blockers**

- reactivation of latent tuberculosis
- demyelination

**Contraindications of usage of TNF- alpha antagonist:**

- Active infection
- Active TB
- MS (Multiple sclerosis)
- Heart failure (NYHA grade 3-4).
- Pregnancy and Breast feeding

### Interleukins: summary

| Cytokine | Main sources | Functions |
|---|---|---|
| **IL-1** | **Macrophages** | Acute inflammation<br>Induces fever |
| **IL-2** | Th1 cells | Stimulates growth and differentiation of T cell response |
| **IL-3** | Activated T helper cells | Stimulates differentiation and proliferation of myeloid progenitor cells |
| **IL-4** | Th2 cells | Stimulates proliferation and differentiation of B cells |
| **IL-5** | Th2 cells | Stimulate production of eosinophils |
| **IL-6** | Macrophages, Th2 cells | Stimulates differentiation of B cells<br>Induces fever |
| **IL-8** | Macrophages | **Neutrophil chemotaxis** |
| **IL-10** | Th2 cells | Inhibits Th1 cytokine production<br>Also known as human cytokine synthesis inhibitory factor and is an 'anti-inflammatory' cytokine |
| **IL-12** | Dendritic cells, macrophages, B cells | Activates NK cells and **stimulates differentiation of naive T cells into Th1 cells** |

### Other cytokines: summary

| Cytokine | Main sources | Functions |
|---|---|---|
| Tumour necrosis factor-α | Macrophages | Induces fever<br>Neutrophil chemotaxis |
| Interferon-γ | Th1 cells | **Activates macrophages** |

**Mnemonic Hot T-Bone stEAk**
- **IL-1**: fever (Hot)
- **IL-2**: stimulates **T** lymphocytes
- **IL-3**: stimulates **Bone** marrow
- **IL-4**: stimulates IgE
- **IL-5**: stimulates IQA

## Immunoglobulin deficiency

The table below summarises the characteristics of the 5 types of immunoglobulin found in the body:

| | | | |
|---|---|---|---|
| IgG | **75%** | Monomer | Enhance **phagocytosis** of bacteria and viruses, **pass to fetal circulation.** |
| IgA | 15% | Monomer/ dimer | Found in **secretions**, provide localized protection on mucous membranes |
| IgM | 10% | **Pentamer** | **First** to be secreted, anti-A, B **blood** antibodies. It is responsible for **haemolytic blood transfusion reactions.** |
| IgD | 1% | Monomer | Involved in **activation of B cells** |
| IgE | **0.1%** | Monomer | Involved in **allergic** reactions anaphylaxis, asthma and atopy.<br>Involved in **type I hypersensitivity** reaction. |

Whilst the majority of IgA is found in secretions there is a significant quantity present in blood. IgE makes up less than 0.1% of immunoglobulins. It is the immunoglobulins which is present in the lowest concentration in blood.

**Total serum IgE** is frequently increased in those with **atopy** but serum IgE does **not** rise **acutely** during an **asthmatic** attack.
**EX**: Patient with **repeated** chest and sinuses infections with **encapsulated** bacteria like Streptococcus pneumoniae and Haemophilus influenzae which should raise the suspicion of **immunoglobulin deficiency (IgA)**.
**IgA deficiency**, in **Caucasians**, is said to occur in **1 in 600-700** individuals. There is often a **deficient response to polysaccharide**-based **vaccinations** such as **HBV** and **tetanus**.

In patients with IgA deficiency, 10-44% of patients **may have anti-IgA antibodies**; this risks a **severe reaction to** IgA-containing products such as blood, plasma or immunoglobulin.

**EX**: Female patient 35 years old, with flu like illness, 10-year history of tendency to have a blocked, stuffy nose and frequent recurrent coughs and colds >>>? **IgA deficiency**.

HIV would be suggested by infections associated with impaired cellular immunity.

## Gamma globulins

### Hypergammaglobulinaemia

#### Causes of polyclonal hypergammaglobulinaemia

- Artefactual, e.g. prolonged venous stasis before venepuncture
- Haemoconcentration secondary to dehydration
- Chronic infection, e.g. TB, infective endocarditis, leishmaniasis
- Autoimmune disease, e.g. SLE, rheumatoid arthritis
- Ulcerative colitis and Crohn's disease
- Sarcoidosis
- Hepatic disease.

#### Causes of monoclonal hypergammaglobulinaemia

- Multiple myeloma, Waldenstrom's macroglobulinaemia and heavy chain disease
- Leukaemia, lymphoma or carcinoma
- Bence Jones proteinuria
- Benign' paraproteinaemia
- Amyloidosis.

### Agammaglobulinemia (e.g., Bruton agammaglobulinemia)

### Hypogammaglobulinemia (low IgG)

- Nephrotic syndrome
- Drug-induced reactions
- Acquired humoral and congenital immunodeficiencies

# Selective IgA deficiency (more details)

The history of mucosal infections (sinus and gastrointestinal) and the family history of immune cytopenia and coeliac disease are suggestive of selective IgA deficiency.

## Definition

- **Most common primary immunodeficiency** that is characterized by a near or total absence of serum and secretory IgA

## Features

- **Often asymptomatic**
- **Recurrent infections**
  - May manifest with sinusitis or respiratory infections (S. pneumoniae, H. influenzae)
  - Chronic diarrhea, partially due to elevated susceptibility to parasitic infection (e.g. by Giardia lamblia)
- **Associated with autoimmune diseases** (e.g., **gluten-sensitive enteropathy**, inflammatory bowel disease, immune thrombocytopenia) and atopy
  - **10-fold increased risk of coeliac disease**
  - Pernicious anaemia and hence gastric carcinoma
  - **Adverse reactions to blood products**
    - Patients with selective IgA deficiency should be tested for the presence of anti-IgA antibodies prior to transfusion with blood products.
- **Anaphylactic reaction to products containing IgA** (e.g., intravenous immunoglobulin)
- **Associated with IgG2 deficiency**
  - **They are more likely than the general population to have an IgG2 deficiency, leading to recurrent bacterial infections**
  - **The possibility of IgG2 deficiency should always be investigated in IgA- deficient individuals with a history of recurrent bacterial infections, but Staphylococcus aureus is the exception**

The Six A's of selective IgA deficiency: Asymptomatic, Airway infections, Anaphylaxis to IgA-containing products, Autoimmune diseases, Atopy

### Diagnosis

- **low serum IgA level, with normal IgG and IgM levels**
- False-positive pregnancy tests

### Treatment

- No specific treatment
- Prophylactic antibiotics
- Intravenous infusion of IgA is not recommended because of the risk of anaphylactic reactions (caused by the production of anti-IgA antibodies).

To prevent transfusion reactions, IgA-deficient patients must be given washed blood products without IgA or obtain blood from an IgA-deficient donor.

## Common variable immunodeficiency (CVID)

**Definition:** primary immunodeficiency with low serum levels of all immunoglobulins despite phenotypically normal B cells

### Epidemiology

- **The most common clinically significant primary immunodeficiency** is CVID.
  - IgA deficiency is more common, but most are asymptomatic.
- Sex: = r3
- Onset: present later than other B cell defects (usually 20-35 years of age)

### Pathophysiology

- Most cases are sporadic with no known family history **(No clear pattern of inheritance)**
- B cells are phenotypically normal but are unable to differentiate into Ig-producing cells, (**B-cell dysfunction**) resulting in low immunoglobulins of all classes.

### Features

- Recurrent pyogenic respiratory infections, e.g., sinopulmonary infections (in rare cases, enteroviral meningitis)
- Associated with a high risk of **lymphoma,** gastric cancer, **bronchiectasis,** and autoimmune disorders (e.g., rheumatoid arthritis, autoimmune hemolytic anemia, immune thrombocytopenia, vitiligo)

## Investigations

- Quantitative immunoglobulin levels: **low levels of IgG, IgA, and IgM**
- Decreased number of plasma cells
- Flow cytometry shows subsets of **normal B and T cells**
- Poor response to immunizations

## Treatment

- **Intravenous immunoglobulin** (IVIG) replacement therapy (**first line**), **the best option to prevent recurrent chest infections.**
- Prophylactic antibiotics

**CVID >> B-cell Cannot differentiate into plasma cells >> low immunoglobulins but normal or decreased B cells.**
**Bruton"s >> Pre-B lvmohocvtes are increased because there's a maturation defect.**

**MRCP part 1 exam: H/O recurrent Giardia lamblia diarrhea and multiple upper respiratory** infections since birth. serum analysis reveals normal levels of mature B lymphocytes. What other finding on serum analysis predisposes the patient to recurrent diarrheal infections?

**>> Deficiency In IgA**

- The patient has **common variable immunodeficiency disorder (CVID)**
- IgA prevent the binding of pathogens to the epithelial cells; thus, preventing protozoa like Giardia lamblia from causing inflammation. Its absence, therefore, leads to the increased likelihood of repeat infection of the GI mucosa

# Severe combined immunodeficiency disease (SCIO)

SCID is due to either a deficiency in IL-2R gamma chain (most common, X-linked) or deficiency in adenosine deaminase (autosomal recessive)

## Overview

- **Numerous genetic mutations>> Combined 8- and T-cell disorder >>** immunodeficiency
- **X-linked recessive** mutations >> defective IL-2R gamma chain receptor linked to JAK3 (most common SCID mutation)
- Autosomal recessive >> Adenosine deaminase deficiency (it aid in breakdown of deoxyadenosine, which is a breakdown product of DNA) >> Accumulation of toxic metabolites **(deoxyadenosine** and dATP) (Deoxyadenosine is toxic to lymphocytes, thus accumulation of this leads to apoptosis of lymphocytes)

## Features (usually manifests in the **first** year of life)

- Recurrent infections
- Diarrhea
- Dermatitis
- Failure to thrive
- Lymph nodes and tonsils may be absent

## Diagnosis

- **Flow cytometry:** absent T cells, abnormal function of B-cells
- CXR: absent thymic shadow
- Lymph node biopsy: absent germinal centers
- 1 Lymphocyte count (< 3000/μL)

## Treatment

- Bone marrow transplantation (the best initial curative treatment)

## Prognosis

- Without intervention, SCIO usually results in severe infection and death in children by age 2 years.

# DiGeorge syndrome

DiGeorge syndrome is a primary immunodeficiency disorder caused by **T-cell deficiency and dysfunction**.
It is an example of a microdeletion syndrome (deletion of a section of chromosome 22).

It is also known as velocardiofacial syndrome and 22q11.2 deletion syndrome and is an autosomal dominant condition.

## Features

- at risk of viral and fungal infections
- parathyroid gland hypoplasia → hypocalcaemic tetany
- thymus hypoplasia
- T-lymphocyte deficiency/dysfunction

It has a variable presentation however its features can be remembered with the mnemonic CATCH22:

- C - Cardiac abnormalities
- A - Abnormal facies
- T - Thymic aplasia
- C - Cleft palate
- H - Hypocalcaemia/ hypoparathyroidism
- 22 - Caused by chromosome 22 deletion

## Investigations

- **Chest X-ray shows absence of the thymic shadow.**
- **Low levels of serum calcium** ($Ca^{2+}$) **and parathormone** (PTH)
- ↓ Absolute T-lymphocyte count
- Delayed hypersensitivity skin testing
- Fluorescence in situ hybridization (FISH) >> Detection of 22q11.2 deletion

**MRCP part 1 exam: In a patient having DiGeorge syndrome, which infection is he most at risk from, secondary to his immune system dysfunction?**
**Cryptococcus neoformans (T-cell dysfunction - ii risk from recurrent viral and fungal infections)**

# Wiskott-Aldrich syndrome (WAS)

**Wiskott-Aldrich syndrome: Classic tetrad of:**

- **Purpura (bleeding diathesis)**
- **Eczema (high risk of atopic disorders)**
- **Recurrent bacterial, viral, and fungal infections (e.g., chest, otitis media)**
- **↑ Risk of autoimmune diseases and hematological malignancies**

## Definition

- Wiskott-Aldrich syndrome (WAS) is defined as an X-linked hereditary disorder associated with adaptive and innate immunodeficiency, micro-thrombocytopenia, eczema, and an increased risk of autoimmune disorders and malignancy.

## Pathophysiology

- "Loss-of-function" mutation in **WASP gene (X-linked recessive inheritance) >>** combined
  **8- and T-cell** dysfunction and thrombocytopenia

**Epidemiology:** occurs primarily in males

## Features

### Classic tetrad

- Purpura (bleeding diathesis)
- Eczema (high risk of atopic disorders)
- Recurrent bacterial, viral, and fungal infections (e.g., chest, otitis media)
- **Increased risk of autoimmline diseases and hematological malignancies** (e.g., lymphoma, leukemia)

## Investigations

- Thrombocytopenia with small platelets
- Low IgM and IgG levels
- ↑ IgE and IgA
- Genetic analysis (confirmatory test): mutated WASp gene

## Prognosis

- The disease has **variable penetrance**, which means that life expectancy can range from 6 - 30 years.

# Complement deficiencies

Complement is a series of proteins that circulate in plasma and are involved in the inflammatory and immune reaction of the body.
Complement proteins are involved in chemotaxis, cell lysis and opsonisation.

## C1 inhibitor (C1-INH) protein deficiency:

- Causes **hereditary angioedema.**
- C1-INH is a multifunctional serine protease inhibitor.
- Probable mechanism is uncontrolled release of bradykinin resulting in oedema of tissues.

## C1q, C1rs, C2, C4 deficiency (classical pathway components):

- Predisposes to **immune complex disease.**
- e.g. **SLE, Henoch-Schonlein Purpura.**

## C3 deficiency:

- Causes **recurrent bacterial** infections.
- Deficiencies of **C3** is more commonly associated with **haemolytic uraemic syndrome**

## C5 deficiency:

- Predisposes to **Leiner disease.**
- Recurrent diarrhoea, wasting and **seborrhoeic dermatitis.**

## C5-9 deficiency:

- Encodes the **membrane attack complex (MAC).**
- Particularly prone to **Neisseria meningitidis** infection.
- **Absent classical and alternate pathway activity**

**EX**: Pt with deficiencies of which one of the complement proteins are most predisposed to **disseminated meningococcal infection?** >> **C5.**
Whilst C3 deficiency is associated with recurrent bacterial infections, **C5** deficiency is more characteristically associated with **disseminated meningococcal infection** and **other Gram negative diplococcal** infections like **Neisseria gonorrhoeae**.

## Membrane attack complex (MAC)

- Formed by C5b, C6, C7, CS, and multiple copies of C9 complement proteins on pathogen cell membranes
- Function >> lyses pathogens
- Inhibited by CD59
  - This exists on body cells to protect them from MAC.
  - paroxysmal nocturnal haemoglobinuria, results in red cells that lack CD59. These red cells can, therefore, be lysed by MAC.

**Decay-accelerating factor (DAF) deficiency is associated with Paroxysmal nocturnal haemoglobinuria PNH.**

### Diagnosis

- **CH50 assay screening test**

**MRCPI part 1 exam: Post splenectomy what type of immunodeficiency is occurs?**

- Humoral
  - Post splenectomy there is increased susceptibility to H. Influenzae, N. Meningitidis and Strep pneumonia which are encapsulated organisms due to the loss of splenic macrophages which are part of the humoral response.

**MRCPUK pat 1 exam:** A 23-year-old man is admitted with sepsis. Blood cultures are reported as *Neisseria gonorrhoeae*. Which complement protein is the patient most likely to deficient in? >> C5-9

# Hypersensitivity

The Gell and Coombs classification divides hypersensitivity traditionally divides reactions into 4 types:

| Type | Mechanism | Examples |
|---|---|---|
| **Type I - Anaphylactic** | Antigen reacts with IgE bound to mast cells (IgE-mediated) | • Anaphylaxis<br>• Atopy (e.g. asthma, eczema and hayfever)<br>Diagnosed by plasma tryptase (protease released from mast cell). |
| **Type II - Cell bound** | IgG or IgM binds to antigen on cell surface (anti booay-rnediated) | • Autoimmune haemolytic anaemia<br>• ITP<br>• Goodpasture's syndrome<br>• Pernicious anaemia<br>• Acute haemolytic transfusion reactions<br>• Rheumatic fever<br>• Pemphigus vulgaris / bullous pemphigoid |
| **Type III - Immune complex** | Free antigen and antibody (IgG, IgA) combine (Immune complex deposition) | • Serum sickness<br>• Systemic lupus erythematosus<br>• Post-streptococcal glomerulonephritis<br>• Extrinsic allergic alveolitis (especially acute phase) |
| **Type IV - Delayed hypersensitivity** | T-cell mediated (cell-mediated) | • Tuberculosis / tuberculin skin reaction<br>• Graft versus host disease<br>• Allergic contact dermatitis<br>• Scabies<br>• Extrinsic allergic alveolitis (especially chronic phase)<br>• Multiple sclerosis<br>• Guillain-Barre syndrome |

In recent times a further category has been added:

| Type | Mechanism | Examples |
|---|---|---|
| **Type V** | Antibodies that recognise and bind to the cell surface receptors.<br>This either stimulating them or blocking ligand binding | Graves' disease<br>Myasthenia gravis |

# Anaphylaxis

Anaphylaxis = type I hypersensitivity reaction
Anaphylaxis - serum tryptase levels rise following an acute episode

**Definition:** a severe type 1 hypersensitivity reaction that can cause life-threatening and multisystem effects due to IgE-mediated mast cell activation

## Pathophysiology

- **Immunoglobulin E is the most common immunoglobulin involved in the pathogenesis of anaphylaxis.**
- Anaphylaxis (type I hypersensitivity reaction) or anaphylactoid reactions >> degranulation of **mast cells** >> massive histamine release >> systemic vasodilation >> increased capillary leakage >> anaphylactic shock
- **Mediators involved in the development of anaphylaxis** include: Tryptase, histamine, leukotrienes, prostaglandins, **IL4**, **IL13**, Heparin and platelet aggregating factor, which are generated by mast cell degranulation.
- **Triggers for anaphylactic reactions:** heat, cold, sexual activity, **exercise**

## Causes

### Anaphylaxis (IgE mediated):

- **Food** (e.g. Nuts) - the most common cause in children
- **Drugs**
  - The most common IgE-mediated triggers are drugs, typically penicillin or other beta-lactam antibiotics.
  - Neuromuscular blocking agents (eg **vecuronium) are responsible for 60- 70% of allergic reactions related to anaesthesia.**
- **Latex**
- **Venom** (e.g. Wasp sting)

### Anaphylactoid (non-IgE mediated).

- The reactions that produce the same **clinical picture** as anaphylaxis **but are not IqE mediated.'**
- plasma proteins or compounds, which act directly on the mast cell membrane, such as

- Vancomycin
- Quinolone antibiotics
- Aspirin or other non-steroidal anti-inflammatory drugs
- Opiates
- Colloid plasma expanders
- Radiographic contrast media

Anaphylaxis following a blood transfusion can be due to immunoglobulin A deficiency.

**Anaphylaxis vs Anaphylactoid**
**Is it anaphylactic OR anaphylactoid reaction?**

| | **Anaphylactic (IgE-mediated anaphylactic reactions)** | **Anaphylactoid (Non IgE-mediated anaphylactic reactions)** |
|---|---|---|
| Is sensitization required? | **Yes** | **No** |
| Can reaction occur in first exposure? | **No** | **Yes** |
| How much exposure is needed to elicit reaction? | very little (dose independent) | usually more than for anaohvlaxis |
| Is reaction predicted by skin allergy test? | **Yes** | **No** |

Which feature is the most important predictor of anaphylaxis in asthmatic patient with peanut allergy? **>> Poorly controlled asthma**

- Poorly controlled asthma is an important risk factor for fatal anaphylaxis in thissituation.
- Patients such as this should have their asthma well controlled and have ready
  access to, and knowledae of how to use, self-iniectable adrenaline.

**Features** (Usually takes 15-30 minutes from the time of exposure to the antigen)

- **Skin or mucous membranes:** Flushing, erythema, pruritus, Swelling of the eyelids, angioedema

- **Respiratory:** hoarseness, Chest tightness, Dyspnea (due to bronchospasm or laryngeal edema), tachypnea, Stridor, wheezing, Hypoxia, cyanosis
- **Gastrointestinal:** Nausea, vomiting (especially in food allergies), Abdominal pain, diarrhea
- **Cardiovascular:** Hypotension, Tachycardia

## Investigations

- **Serum mast-cell tryptase: if elevated, supports the diagnosis of anaphylaxis**
  - has a half-life of 2 h, peaking at 1 h after anaphylaxis onset and return to baseline by 6 hours.
  - Both sensitivity and specificity to confirm diagnosis is 95%
  - **Normal tryptase results do not exclude anaphylaxis**
- Complement C4 levels: can be low in hereditary angioedema
- Total serum IgE level is **non-specific and unhelpful.**

## Management

- Airway assessment and management: Rapid sequence intubation (RSI) for airway compromise
- **Adrenaline**
  - the most important drug in anaphylaxis and **should be given as soon as possible.**
  - The dose for **adult and child > 12 years**: 500 micrograms (0.5ml **1 in 1,000**)
  - The best site for IM injection is the anterolateral aspect of the middle third of the thigh.
  - Adrenaline can be repeated every 5 minutes if necessary.
- Hydrocortisone 200 mg
- Chlorphenamine 10 mg
- IV fluids
  - Evidence from a large randomised controlled trial (RCT) suggests there is no difference between normal saline and Hartmann's solution [also known as Ringer's lactate] for resuscitation of critically ill patients.
- Observation: It is recommended to observe patients after resolution of an anaphylactic episode for 24 hours **for possible second-phase reactivation.**

**Late-phase reaction**

**In IgE mediated reactions such as asthma or anaphylaxis what therapy inhibits the important late-phase reaction? >> steroids**

- The late phase reaction is due to attraction of T cell, release of leukotrienes and prostaglandins often characterised by asthma
- prevented by the administration of steroids (**Hydrocortisone**).
- Approximately **30% of deaths related to anaphylaxis occur as a consequence of this late-phase reaction**

**Epinephrine injections for anaphylaxis should always be given intramuscularly in a concentration of 1:1,000 (as opposed to the 1:10,000 solution used in cardiac arrest). Injecting the 1:1,000 solution into a vein can lead to cardiac arrhythmia/arrest.**

**Antihistamines and steroids should be administered in anaphylaxis only after the initial resuscitation measures (IM epinephrine, fluids and/or vasopressors) have been given.**

**A lack of response to epinephrine, antihistamines, and steroids should raise suspicion of differential diagnoses such as bradykinin-mediated angioedema, which requires its own specific treatment**

## Exercised induced anaphylaxis

a rare disorder in which anaphylaxis occurs after physical activity.

**Features:** usually **occur around 10 minutes after exercise** and follow a sequence of pruritus, widespread urticaria and then subsequently respiratory distress and vascular collapse.

**Pathophysiology:** may be related to **endorphin release during exercise**. The endorphin causes excessive histamine release from mast cells in susceptible individuals.

**Associations**

- Co-factors such as foods, alcohol, temperature, drugs (eg, aspirin and other nonsteroidal anti-inflammatory drugs), humidity, seasonal changes, and hormonal changes are important in the precipitation of attacks.
- most associated with wheat ingestion.
- The foods most commonly implicated in food-dependent exercise-induced anaphylaxis are wheat, shellfish, tomatoes, peanuts, and corn.

- The patients can usually eat the causative food without problems so long as they do not exercise afterwards.

### Treatment

- managed in the same manner as anaphylaxis.
- usually resolves on stopping exercise
- Reducing physical activity to a lower level may diminish the frequency of attacks.
- **Patients should be instructed on the proper use of emergency injectable epinephrine** and have one available at all times.
- Patients should wear a medical alert bracelet with instructions on the use of epinephrine.

## Anaphylactic reactions associated with anesthesia

### Risk factors

- Neuromuscular blocking drugs and latex appear to cause anaphylaxis more commonly in female patients
- Individuals with a **history of atopy, asthma or allergy to some** foods appear to be at **increased risk of latex allergy** **but not anaphylaxis to neuromuscular blocking drugs or antibiotics**
- Patients with **asthma** or taking **b-blocking drugs** may suffer a more severe reaction.

### Causes

#### Neuromuscular blocking agents (NMBAs)

- **Most common cause**
- **60% of cases of anaesthesia-related anaphylaxis are due to neuromuscular blocking agents.**
- 80% of NMBA reactions occur without prior exposure
- Quaternary ammonium ions (QAI) are proposed to be the allergenic epitopes in NMBAs.
- Common environmental chemicals such as toothpastes, washing detergents, shampoos, and **cough medicines** share these allergenic epitopes with the NMBAs, predisposed individual to become sensitised to QAIs and thus be at **risk of developing anaphylaxis to NMBAs during anaesthesia.**
- **succinylcholine** is the NMBA **most likely** to be associated with **allergic anaphylaxis** (carries the highest risk)

### Latex

- Latex hypersensitivity is the second most common cause of anaesthesia related anaphylaxis in many studies (up to 20% of cases). **But now decreased due to decline in the use of latex gloves.**

### Antibiotics

- Approximately 15% of anaesthesia-related anaphylactic episodes are due to **antibiotics.**
  - Skin testing is only approximately 60% predictive of clinical hypersensitivity. Penicillins and
  - cephalosporins which share the b-lactam ring are responsible for approximately 70% of antibiotic-induced anaphylaxis.
  - There is a higher rate of antibiotic allergy in smokers

### Anaesthetic induction agents

- Anaphylaxis to **propofol is very uncommon**
- Anaphylaxis to thiopental has become extremely uncommon, probably reflecting the decline in its use.

### Antiseptics and disinfectants

- Reactions to **chlorhexidine** have come into greater prominence in recent years.
- Anaphylaxis has occurred when chlorhexidine was used as an antiseptic for urological and gynaecological procedures as well as insertion of central venous and epidural catheters.
- Allowing chlorhexidine to dry before beginning a procedure may reduce the risk of reaction.
- Anaphylaxis to other antiseptics is rare.

## Diagnosis

### Timings

- Type I reactions typically occur within **seconds to minutes** after **i.v. exposure.**
- An insidious or delayed onset may occur (e.g. with latex, antibiotics, and colloids and a tourniquet may delay onset until after surgery).

**History of atopy and asthma has a clear link with latex allergy.**

# Serum Sickness

**Definition:** Serum sickness is a classic example of a **type III hypersensitivity reaction**, which usually develops as a complication of antitoxin or antivenom administration.

## Aetiology

- Antivenom or antitoxin containing animal proteins
- Medications most frequently antibiotics (e.g., penicillin, amoxicillin, cefaclor, trimethoprim- sulfamethoxazole)
- Infections: Hepatitis B virus

## Pathophysiology

- exposure to an antigen (e.g., antivenom, drug)-+ formation of antibodies-+ deposition of antibody-antigen complexes in tissue -+ activation of the complement cascade -+ tissue damage and systemic inflammation

## Features

- Symptoms appear 1-2 weeks following initial exposure (because antibodies take several days to form), and usually resolve within a few weeks after discontinuation of the offending agent.
- Fever
- Rash (urticaria! or purpuric)
- Arthralgias
- Lymphadenopathy

### Subtypes and variants: serum sickness-like reaction

- much more common than actual serum sickness
- Aetiology: similar to that of serum sickness
- Infections (e.g., hepatitis B, rabies)
- Medications that can act as haptens (e.g., allopurinol, cephalosporins, penicillin).

**Diagnostics:** Urinalysis may show mild **proteinuria.**

**Treatment:** Stop the offending agent.

# Basics of electrolytes and acid base disorders

## Osmolality and Osmolarity

The **osmolar gap** is the difference between the **calculated osmolarity** and the **measured osmolality**.

Osmolar gap= Calculated Osmolarity (Osmol/**L**) – Lab Osmolality (Osmol/**Kg**)

The normal value is **10-15** but may be increased in the presence of unmeasured 'abnormal' osmotically active ions in the plasma.

**Osmolarity** is the measure of solute concentration, defined as the number of osmoles (Osm) of solute per litre (l) of solution (**Osmol/l**).

**Calculated osmolarity = 2 (Na + K) + Glucose + Urea (all in mmol/L).**

2 (132 + 4) + 5 + 7 = 306 mOsm/L

**Normal serum osmolarity is 285-295 mOsm/L.**

**Osmolarity can be** affected by temperature and pressure and for a given solution, this calculated variable is less than the osmolality.

**Osmolality** is also a measure of solute concentration but is defined as the number of osmoles (Osm) of solute per kilogram (**Osm/Kg).**

The value is independent of temperature and pressure. It is measured in the **laboratory** using an **osmometer**. Osmometers use the colligative properties of a solution such as depression of freezing point or vapour pressure.

Osmolar gap= Osmolality − osmolarity = 324 − 284 = 40

An elevated osmolar gap provides indirect evidence for the presence of an **abnormal solute** that may be present in significant amounts.

To have much effect on the osmolar gap, this substance needs to have a low molecular weight and be uncharged so it can be present in a form and in a concentration (measured in mmol/l) sufficient to elevate the osmolar gap.

**Ethanol**, **ethylene glycol** (anti-freeze), **acetone** and **methanol** are solutes that will cause elevation of the osmolar gap in this way.

# Anion gap (AG)

**Renal tubular acidosis causes a normal anion gap**

- The anion gap allows for the differentiation of 2 groups of metabolic acidosis.
  - **Metabolic acidosis with a high AG** is associated with the **addition of** endogenously or exogenously **generated acids**.
  - **Metabolic acidosis with a normal AG** is associated with the **loss of $HCO_3$ or the failure to excrete $H^+$ from the body.**
- The anion gap is calculated by: (sodium + potassium) - (bicarbonate + chloride)
- A normal anion gap is **8-14 mmol/L**
- **It is useful to consider in patients with a metabolic acidosis:**
  - **Causes of a normal anion gap or hyperchloraemic metabolic acidosis**
    - gastrointestinal bicarbonate loss: diarrhoea, uretero-sigmoidostomy, fistula
    - **renal tubular acidosis**
    - **drugs: e.g. acetazolamide**
    - ammonium chloride injection
    - Addison's disease
  - **Causes of a raised anion gap metabolic acidosis**
    - lactate: shock, hypoxia
    - ketones: diabetic ketoacidosis, alcohol
    - urate: renal failure
    - acid poisoning: salicylates, methanol

**mnemonic of high anion gap acidosis:**
**DR. MAPLES**: D-DKA; R-renal; M-methanol; A-alcoholic ketoacidosis; P-paraldehyde, phenformin; L-lactic (ie, CO, HCN); E-ethylene glycol; S-salicylates

Remember the mnemonic MUDPILES >> high anion gap acidosis

| | |
|---|---|
| **M** | Methanol |
| **U** | Uremia |
| **D** | Diabetic ketoacidosis |
| **P** | Paraldehyde |
| **I** | Infection |
| **L** | Lactic acidosis |
| **E** | Ethylene glycol |
| **S** | Salicylates |

**Metabolic acidosis associated with bladder reconstruction (e.g: for carcinoma of the bladder).**

- Hyperchloraemic metabolic acidosis is a documented complication of neobladder formation. However, it usually improves with time and is mild.
- Severe and persistent metabolic acidosis may manifest when patients undergo further surgery for other reasons, as is the case in this patient.
- Neobladder formation following radical cystectomy or cystoprostatectomy is becoming increasingly more common, and medical staff treating patients with neobladders should recognise and **treat metabolic acidosis with intravenous fluids and bicarbonate**.

In **normal** anion gap metabolic acidosis, **chloride** is **retained** to balance the charge of the HCO3 ions, which are lost. So it is also called **hyperchloraemic** metabolic acidosis. (Chloride N= 95-110 mmol/L).

| **Normal** anion gap (=**hyperchloremic** metabolic acidosis) | **Raised** anion gap |
|---|---|
| 1) **HCO3 loss** from **GIT**: diarrhoea, ileostomy, ureterosigmoidostomy, fistula.<br>2) **HCO3 loss** from **kidneys:**<br>o **RTA** (type **2**) (proximal).<br>o **Drugs**: e.g. **acetazolamide**.<br>o **Tubular damage**.<br>o **Hyperparathyroidism.**<br>**3) Decreased H+ ion excretion from the kidneys:**<br>o **RTA** (type **1**) (distal).<br>o **RTA** (type **4**).<br>4) **Ammonium chloride** injection.<br>5) **Addison's** disease. | 1) **DKA.**<br>**2) Renal failure.**<br>3) **Salicylates** poisoning.<br>4) **Alcohol, methanol, Ethylene glycol**<br>5) **Lactic acidosis**: type A&B. |

Metabolic acidosis secondary to high lactate levels is subdivided into two types:

- Lactic acidosis **type A**: shock, hypoxia, burns.
- Lactic acidosis **type B**: drugs: Metformin, TCA.

# Metabolic alkalosis

Metabolic alkalosis may be caused by a loss of hydrogen ions or a gain of bicarbonate. addison

It is due mainly to problems of the kidney or gastrointestinal tract.

Alkalosis is more unusual clinically than acidosis and has fewer causes.

Maintaining an alkalosis is also more difficult as the body produces significant amounts of acid each day during normal metabolism.

## Causes:

- Hypokalaemia (see next)
- **Vomiting / aspiration** (e.g. anorexia nervosa, peptic ulcer leading to pyloric stenos, gastric outlet obstruction, **nasogastric suction**)
- **Diuretics**
- **Burns**
- **Liquorice, carbenoxolone**
- **Conn's (Primary hyperaldosteronism)**
- **Cushing's** syndrome
- **Bartter's** syndrome
- **Congenital adrenal hyperplasia**

## Mechanism of metabolic alkalosis:

- Activation of renin-angiotensin II-aldosterone (RAA) system is a key factor.
- Aldosterone causes reabsorption of $Na^+$ in exchange for H+ in the distal convoluted tubule.
- ECF depletion (vomiting, diuretics) → $Na^+$ and Cl- loss → activation of RAA system → raised aldosterone levels.
- In hypokalaemia, $K^+$ shift from cells → ECF, alkalosis is caused by shift of H+ into cells to maintain neutrality.

# Respiratory acidosis

## Causes

| Mechanism | Causes |
|---|---|
| **Acute respiratory acidosis** | Acute lung disease (e.g., pneumonia , pulmonary edema)<br>Acute exacerbation of chronic obstructive airway disease (e.g., COPD, asthma)<br>**CNS depression due to:**<br>• Head trauma<br>• Postictal state<br>• Drug toxicity (e.g., from opiates, barbiturates, benzodiazepines)<br>• Central sleep apnea |
| **Chronic respiratory acidosis** | **Airway obstruction (e.g., COPD, asthma)**<br>**Respiratory muscle weakness, e.g., due to:**<br>• Myasthenia gravis<br>• ALS<br>• Guillain-Barre syndrome<br>• Poliomyelitis<br>• Multiple sclerosis<br>• Severe hypokalemia |

## Features

| Signs and symptoms of respiratory acidosis | | |
|---|---|---|
| **Central nervous system** | **Respiratory system** | **Cardiovascular system** |
| Cerebral vasodilation | Breathlessness | Flushing, bounding pulse |
| Increased intracranial pressure | Cyanosis | Cor pulmonale |
| Headache, confusion, agitation | Pulmonary hypertension | Systemic hypotension |
| Hallucinations, transient psychosis | | Arrhythmias |
| Myoclonic jerks, flapping tremor, extensor plantars, depressed reflexes | | Initially good cardiac output, then decreases |
| Papilloedema, constricted pupils | | |
| Seizures, coma | | |

## Respiratory alkalosis

### Causes of respiratory alkalosis:

- Central causes - stroke, meningitis, CNS tumour
- Drugs - salicylates
- Anxiety
- Pregnancy.

### ABG picture

- pH: elevated
- PC02: low
- HC03: Expected compensatory response: ↓

### Differential diagnosis of respiratory alkalosis with type 1 respiratory failure (low p02 and low pC02.):

- Chronic venous thromboembolism (most likely).
- Pulmonary fibrosis (but basal crackles may be expected).

## Hypokalemia and acid-base balance

Potassium and hydrogen can be thought of as competitors.

Hyperkalaemia tends to be associated with **acidosis** because as potassium levels rise fewer hydrogen ions can enter the cells.

| Hypokalaemia with acidosis: | Hypokalaemia with alkalosis: |
|---|---|
| 1) **Partially treated DKA** | 1) **Vomiting** |
| 2) **Renal tubular acidosis** | 2) **Diuretics** |
| 3) **Diarrhoea** | 3) **Cushing's** syndrome |
| 4) **Acetazolamide** | 4) **Conn's** syndrome |

**Magnesium deficiency** may also cause hypokalaemia. In such cases, normalizing the potassium level may be difficult until the magnesium deficiency has been corrected.

Approximately a **drop of 1 mmol in serum potassium** is equivalent to **a total body loss of 200 mmol of potassium.**

# Hyperkalaemia

Plasma potassium levels are regulated by a number of factors including aldosterone, acid-base balance and insulin levels.

**Metabolic acidosis** is associated with **hyperkalaemia** as hydrogen and potassium ions compete with each other for exchange with sodium ions across cell membranes and in the distal tubule.

**ECG** changes seen in hyperkalaemia include **tall-tented T waves**, small P waves, **prolonged PR interval**, **widened QRS** leading to a sinusoidal pattern and asystole.

## Causes of hyperkalaemia:

- **Firstly exclude pseudo-hyperkalaemia** >> Re-check a fresh sample.
- **Acute renal failure**
- **Metabolic acidosis**
- **Addison's**
- **Rhabdomyolysis**
- **Massive blood transfusion**
- **Drugs**: **Aldactone**, **ACEIs**, **ARBs**, **Cyclosporine**, **Heparin** (UFH & LMWH), **Beta blockers**.

Both **UFH** and **LMHH** can cause hyperkalaemia. This is thought to be caused by inhibition of aldosterone secretion.

**Beta-blockers** interfere with potassium transport into cells and can potentially cause hyperkalaemia in renal failure patients - remember beta-agonists, e.g. Salbutamol, are sometimes used as emergency treatment.

**Psudohyperkalaemia** is known to be associated with **essential thrombocytosis**, and patients with essential thrombocytosis are at increased risk of **gout**, and any prescription of **Lasix** will only make the problem worse.

## Foods that are high in potassium:

- Salt substitutes (i.e. contain potassium rather than sodium).
- **Bananas**, **oranges**, **kiwi** fruit, **avocado**, **spinach**, **tomatoes**.

The most appropriate initial therapy of hyperkalaemia is **protection of the heart** by **IV calcium gluconate** which acts within **minutes** and works by **raising the depolarization threshold for myocytes**.

Other medical treatment to lower K level (cell shift) is: **15 units actrapid insulin in 50 ml dextrose 50%, salbutamol nebulizer, NaHCO3 IV** (debatable, can worse volume overload esp. in renal imp and pulmonary oedema).

**Calcium resonium** is an **ion exchange resin** which, when taken orally, prevents potassium from being absorbed in the diet. It acts to deplete the body of potassium (by preventing absorption) and **takes at least 24-48 hours to have an effect.** It is not suitable as an emergency treatment.

Guidelines for **surgery** in patients with **CRF** suggest that surgery should be postponed **until serum K below 5.5 mmol/l** and also K should be monitored **immediately** after surgery and then again **4-6 hours later**.

**May 2020 exam: H/0 muscle weakness and lethargy. K+ = 6.3 mmol/l. What is the most appropriate initial treatment to lower the serum potassium level?**
**-+ Insulin/dextrose infusion**

## Pseudohyperkalaemia

High cell counts and high potassium: consider pseudohyperkalaernia

### Causes

- Haemolysis during venepuncture or tight torniquet.
- Delay in the processing of the blood specimen
- Abnormally high numbers of platelets, leukocytes, or erythrocytes (such as myeloproliferative disorders or **essential thrombocytosis)**
- Familial causes

### Management

- **Re-check a fresh sample at the hospital and do LDH to exclude hemolysis.**
- Measuring an arterial blood gas will give a quick and accurate measure of true serum potassium.

# Hyponatremia

Hyponatraemia may be caused by water excess or sodium depletion.

**Causes** of **pseudohyponatraemia** include (High blood **lipid** or **protein**):

- **Hyperlipidaemia** (increase in serum volume) as in nephrotic syndrome or
- **Hyperproteinaemia** as in myeloma.
- **Taking blood from a drip arm.**

Urinary sodium and osmolality levels aid making a diagnosis.
It is important to diagnose pseudohyponatraemia, **because as the plasma osmolality is normal no treatment is required.**

**Urinary sodium > 20 mmol/l:**

**Sodium depletion, renal loss (patient often hypovolemic):**

- Addison's
- Diuretics
- Diuretic stage of renal failure

**Patient often euvolaemic:**

- SIADH (urine osmolality > 500 mmol/kg)
- Hypothyroidism

**Urinary sodium < 20 mmol/l:**

**Sodium depletion, extra-renal loss:**

- Diarrhoea, vomiting, sweating
- Burns, adenoma of rectum

**Water excess (patient often hypervolaemic and oedematous):**

- Secondary hyperaldosteronism: heart failure, cirrhosis.
- Reduced GFR: renal failure.
- IV dextrose, psychogenic polydipsia.

| In Hyponatraemia >>>>> Check Urinary NA | | | |
|---|---|---|---|
| **Urinary sodium > 20 mmol/l** | | **Urinary sodium < 20 mmol/l** | |
| **Hypovolemic** (Na depletion, **Renal** loss) | **Euvolaemic** | **Hypervolaemic** | **Hypovolemic** (Na depletion, **Extra-renal** loss) **(as pre-renal azotaemia)** |
| • Addison's.<br>• Diuretics.<br>• Diuretic stage of ARF. | • **SIADH**: (High urine osmolality > 500 mmol/kg)<br>• Hypothyroidism | • Secondary hyperaldosteronism: CHF, L cirrhosis, Nephrotic S.<br>• Reduced GFR: renal failure.<br>• Psychogenic polydipsia.<br>• IV dextrose. | • Diarrhoea.<br>• Vomiting.<br>• Sweating.<br>• Burns.<br>• Adenoma of rectum. |

**Beer potomania** is a recognized cause of **hyponatraemia** in **alcohol misusers**, there is **osmolar gap** due to presence of osmotically active ethanol in the blood, and the electrolyte imbalance **normally corrects** itself with **cessation** of alcohol.

Patients with chronic liver disease and ascites often develop hyponatraemia, the management of which can be difficult.

Diuretic therapy for the management of ascites often contributes to the hyponatraemia.

The British Society of Gastroenterology guidelines suggest that where the **serum sodium is ≤120 mmol/L >>> diuretic therapy should be stopped** and **give** the patients **volume expansion** with **colloid** or **normal saline**.

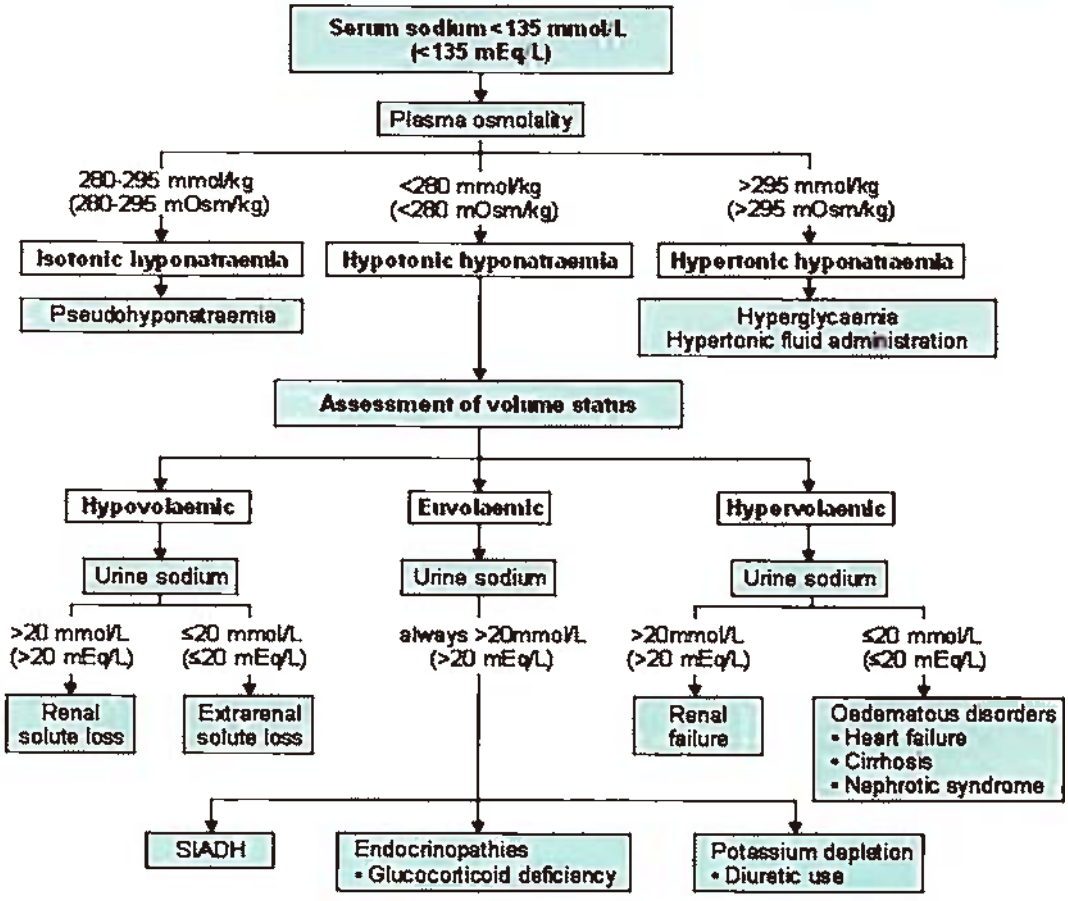
No specific intervention other than careful **monitoring** is advised where the serum sodium is **126-135** mmol/L.

In the range **121-125** mmol/L where the serum creatinine is normal, **diuretic** therapy may be continued but may need to be **reduced** with a view to stopping if necessary.

If the sodium is in this range but the serum creatinine is rising diuretics should be stopped and patients should receive volume expansion.

These guidelines also advise that **fluid restriction** should only be used in patients who are clinically **euvolaemic**, **not on diuretics** and have severe hyponatraemia with a normal serum creatinine.

**EX**: Pt. with CLD and ascites on diuretics with serum Na 115 mmol/L >>> **Stop diuretics and give normal saline.**



## SIADH (The syndrome of inappropriate ADH secretion)

SIADH is characterised by **hyponatraemia** secondary to the **dilutional effects** of **excessive water retention.**

### Criteria:

- **Normal Renal, Normal Adrenal and Normal Thyroid.**
- Hyponatraemia < 135 mEq/l
- Hypotonic plasma **P**osmo < 270 mOsm/Kg
- Inappropriate ↑ urine osmolality
- ↑ Urine Na > 20 mEq/L

### Causes of SIADH:

| Category | Examples |
|---|---|
| **Malignancy** | • **Small cell lung cancer (SCLC)**<br>• also: pancreas, prostate |
| **Neurological** | • Stroke<br>• Subarachnoid haemorrhage<br>• Subdural haemorrhage<br>• Meningitis/encephalitis/abscess |
| **Infections** | • Tuberculosis<br>• Pneumonia |
| **Drugs** | • **Sulfonylureas**<br>• **SSRIs**<br>• **TCA**<br>• **Carbamazepine**<br>• **Thiazide**<br>• Vincristine<br>• Cyclophosphamide |
| **Other causes** | • Positive end-expiratory pressure (PEEP)<br>• **Porphyrias** |

## Management:

- Correction must be done **slowly** to **avoid** precipitating **central pontine myelinolysis (CPM).**
- **Fluid restriction.**
- **Demeclocycline oral:** reduces the responsiveness of the collecting tubule cells to ADH >> **it will induce nephrogenic D.I.** it is used for SIADH when fluid restriction alone is inadequate.
- **ADH (vasopressin) receptor antagonists** have been developed.

**NB:** Lithium induces nephrogenic DI but is not an appropriate ttt for SIADH.

**N.B: Other points to diagnose SIADH:**

- Maintained hypervolemia.
- Suppression of RAS (renin angiotensin system)
- No equal concentration of ANP (atrial natriuretic peptide)
- Normal serum creatinine.
- Normal acid base and K balance.
- ↓ BUN
- ↓ Uric acid
- ↓ Albumin

# Antidiuretic hormone (ADH)

ADH is a **nona-peptide** **manufactured** in the **supra-optic (SO)** and **paraventricular (PV) nuclei** of the **hypothalamus** and **released (secreted)** from the **posterior** pituitary.

It **acts on** the **collecting ducts** improving water permeability and hence water retention.

It promotes water reabsorption in the collecting ducts of the kidneys by the **insertion of aquaporin-2 channels.**

Carbamazepine as well as other agents such as thiazides and SSRIs may potentiate its release.

Ethanol usually inhibits release.

Antidiuretic hormone (ADH) >>> site of action >>> collecting ducts

| | Notes | Further detail |
|---|---|---|
| **Source** | Synthesized in the supraoptic nuclei of the hypothalamus, released by the posterior pituitary | |
| **Function** | Conserves body water | Promotes water reabsorption in the collecting ducts of the kidneys by the insertion of aquaporin-2 channels |
| **Regulation** | Increases secretion<br>extracellular fluid osmolality increase<br>volume decrease<br>pressure decrease<br>angiotensin II<br>Decreases secretion<br>extracellular fluid osmolality decrease<br>volume increase<br>temperature decrease | Diabetes insipidus (DI) is a condition characterised by either a deficiency of antidiuretic hormone, ADH, (cranial DI) or an insensitivity to antidiuretic hormone (nephrogenic DI) Cranial DI can be treated by desmopressin, an analog of ADH |

## Hypernatremia

### Causes of hypernatraemia:

- **Severe Dehydration.**
- **Diabetes insipidus.**
- Osmotic diuresis e.g. **Hyperosmolar** non-ketotic diabetic coma (HHS).
- **Excess IV saline**

Hypernatremia should be corrected with great caution.

Although brain tissue can lose sodium and potassium rapidly, lowering of other osmolytes (and importantly water) occurs at a slower rate, predisposing to cerebral oedema, resulting in seizures, coma and death.

Although there are no clinical guidelines by NICE or Royal College of Physicians at present, it is generally accepted that **a rate of no greater than 0.5 mmol/hour correction is appropriate**.

**EX:** A 74-year-old gentleman with **dementia** is admitted from the nursing staff, with worsening confusion and inability to eat and drink.
He is clinically dehydrated and his **serum Na** is measured at **168** mmol/litre. Assuming the normal serum sodium value is 140 mmol/litre, and **his total body water is 40 litres**, calculate the free water deficit.
**The free water deficit in litre calculation** is as follows:
(Patient sodium-140)/ 140) x total body water (TBW) = free water deficit in litres.
(168-140/140) X 40 = **8 litres**.

## Hypomagnesaemia

### Cause of low magnesium:

- **Diuretics**
- Diarrhoea
- TPN (Total parenteral nutrition)
- Alcohol
- Hypokalaemia, Hypocalcaemia

### Features:

- Paraesthesia
- Tetany
- Seizures
- Arrhythmias
- Decreased PTH secretion → hypocalcaemia
- ECG features similar to those of hypokalaemia
- Exacerbates digoxin toxicity

## Hypophosphatemia

### The three major mechanisms of hypophosphatemia are:

- **Redistribution** of extracellular phosphate into cells
- Decreased **intestinal absorption** and
- Depletion due to increased **urinary loss**

### Causes:

- **Alcohol excess**
- **Acute liver failure**
- **Primary hyperparathyroidism**
- **Osteomalacia**
- **Hyperventilation**
- **DKA**
- **Refeeding syndrome**

### Consequences:

- Red blood cell haemolysis
- White blood cell and platelet dysfunction
- Muscle weakness and rhabdomyolysis
- Central nervous system dysfunction

**EX**: A 19-year-old female with a history of **anorexia nervosa** is admitted to hospital. Her BMI has dropped to 16. She has agreed to be fed by **nasogastric tube (NGT).** Which one of the electrolyte disturbances is most likely to occur?
>>> This patient is at risk of **refeeding syndrome**, which can lead to **profound hypophosphatemia.**

**Refeeding syndrome** occurs when **malnourished** individuals are given nutritional support (or simply recommence food intake).

Individuals need only to have been starved for as little as 5 days to be at risk.

Patients may present with symptoms ranging from weakness to alterations in mental state, neurological abnormalities (dysarthria, diplopia) and rhabdomyolysis.

The **triad of electrolyte** abnormalities of (**K**, **Mg**, and **Po4**), **hypokalaemia, hypomagnesaemia** and **hypophosphatemia** are characteristic.

**Management:**
**1) Correcting electrolyte abnormalities** aggressively IV or orally.
**2)** Carefully controlling calorific intake: **Calorie intake may need to be reduced** to less than 50% of the recommended amount.

**NB**: Supplementary **NG** feeding is usually **NOT** indicated.
**NB**: **TPN** does **NOT** offer any significant advantage over oral feeding and is associated with significant complications; where there is an intact gut feeding should be via this route.

When a patient **hyperventilates**, there is a rise in intracellular pH (fall in partial pressure of carbon dioxide, which can readily diffuse across cell membranes). The rise in pH then stimulates phosphofructokinase activity, which in turn activates glycolysis.
So, **painful venepuncture** >> **Hyperventilation** >> **low serum Phosphate**

**Oncogenic hypo-phosphataemic osteomalacia** and **x linked hypophosphataemic rickets** belong to the third mechanism of urinary excretion.

**MRCPUK part 1**: what is the mechanism of Hypophosphataemia during treatment of DKA? **>> Shift from extracellular to intracellular space**

**MRCPUK part 1: what is the mechanism of Hypophosphataemia in alcoholic patients after hospital admission?**

- **Shift from extracellular to intracellular space**
  - The alcoholic patient often has chronic phosphate depletion, and, after admission to the hospital, is prone to severe hypophosphatemia resulting from redistribution of extracellular phosphate into the cells.
  - Two factors may contribute to this shift:
    1. I.V therapy with dextrose-containing solutions or refeeding >> ↑Glucose >> ↑ insulin release >> ↑ phosphate uptake by the cells
    2. alcohol withdrawal >> hyperventilation >> acute respiratory alkalosis >> intracellular alkalosis >> stimulates intracellular phosphofructokinase >> ↑ glycolysis >> movement of phosphate into cells

## Hyperphosphatemia

- The healthy adult usually ingests about **8400 mg per week of phosphate through their diet**
- **Absorption** occurs mainly in the jejunum
- **Renal absorption** the **majority** (70%) of filtered phosphate is reabsorbed by **type 2a sodium phosphate cotransporters** located on the apical membrane of the renal **proximal tubule**.
- **The normal** adult range for phosphorus is 2.5-4.5 mg/dL (0.81-1.45 mmol/L).
- **Renal excretion: About 5400 mg of phosphate is excreted per week through the kidneys.**

### Causes

- usually iatrogenic
- rhabdomyolysis
- ↓calcium + ↑ phosphate levels seen in: **(decreased phosphate excretion)**
  - **renal failure,**
  - hypoparathyroidism, and pseudohypoparathyroidism
- ↑calcium + ↑phosphate seen in:
  - vitamin D intoxication (↓PTH + ↑ vitamin D)
  - milk-alkali syndrome (↓PTH + ↓vitamin D)
- **Disorder that shifts intracellular phosphate to extracellular space**
  - Tumor lysis
  - Rhabdomyolysis
- **Increased phosphate intake** (e.g., phosphate-containing enemas)

- Laxative (Phospho-soda) abuse
- **Foods that are characteristically rich in phosphate include:** **dairy products, (Cheddar cheese),** fibre rich foods, chocolate, and processed meats.

## Features

- Often asymptomatic
- High P043- levels cause the formation of an insoluble compound with calcium, which can lead to:
  - Hypocalcemia >> hypocalcemic symptoms (muscle cramps, tetany, and perioral numbness or tingling).
  - Nephrolithiasis
  - Calcifications in the skin

## Management

- Treat the underlying cause.
- Discontinue phosphate intake (dietary or medication).
- Give phosphate binders (e.g., aluminium hydroxide, calcium carbonate).
- Consider dialysis (especially in severe cases of hyperphosphatemia in patients with renal failure).

# Genetic and synthesis inherited diseases

## Tumor suppressor genes

### Basics:

- Genes which **normally control the cell cycle.**
- Loss of function results in an increased risk of cancer.
- Both alleles must be mutated before cancer occurs.

### Examples:

| Gene | Associated cancers |
|---|---|
| **p53** | Common to many cancers as **Li-Fraumeni syndrome** |
| **APC** | Colorectal cancer |
| **BRCA1 & BRCA2** | Breast and ovarian cancer<br>In men, there is an increased risk of breast cancer and **prostate cancer** |
| **NF1** | Neurofibromatosis |
| **Rb** | Retinoblastoma |
| **WT1** | Wilm's tumour |
| Multiple tumor suppressor 1 (MTS-1, p16) | Melanoma |

**Tumour suppressor genes**: ***loss*** of function results in an **increased** risk of cancer.
**Oncogenes**: ***gain*** of function results in an **increased** risk of cancer.

example of >>> **Western blotting**

## P53 gene

P53 is a **tumour suppressor gene** located on chromosome **17p**.

It is the most commonly mutated gene in **breast**, **colon** and **lung** cancer.

P53 is thought to play a crucial role in the cell cycle, preventing entry into the S phase until DNA has been checked and repaired. It may also be a key regulator of **apoptosis.**

**Li-Fraumeni syndrome** is a **rare autosomal dominant** disorder characterised by the early onset of a variety of cancers such as **sarcomas** and **breast** cancer. It is caused by **mutation in the p53 gene**.

## Oncogenes

**Oncogenes** are endogenous human deoxyribonucleic acid (DNA) sequences that arise from normal genes called proto-oncogenes.

**Proto-oncogenes** are normally expressed in many cells, particularly during fetal development, and are thought to play an important regulatory role in cell growth and development.

Alterations in the proto-oncogene can activate an oncogene, which produces unregulated gene activity, contributing directly to tumourogenesis.

**Oncogene alterations are important causes of:**

- **Rhabdomyosarcomas** (**ras** oncogene)
- **Burkitt's lymphoma** (**C-myc** is translocated intact from its normal position on chromosome 8 to chromosome 14)
- **Neuroblastoma** (**N-myc** proto-oncogene is seen in a proportion of patients with poor prognosis).

They should be contrasted with tumour suppressor genes. In this situation, the genes normally down regulate cell growth, and require inactivation to allow malignant growth. Examples include retinoblastoma.

### Examples

| Gene | Category | Associated cancers |
|---|---|---|
| **ABL** | Cytoplasmic tyrosine kinase | **Chronic myeloid leukaemia** |
| **c-MYC** | Transcription factor | **Burkitt's lymphoma** |
| **n-MYC** | Transcription factor | **Neuroblastoma** |
| **BCL-2** | Apoptosis regulator protein | **Follicular lymphoma** |
| **RET** | Tyrosine kinase receptor | **Multiple endocrine neoplasia (types II and III)** |
| **RAS** | G-protein | Many cancers especially **pancreatic** |
| **erb-B2 (HER2/neu)** | Tyrosine kinase receptor | Breast and ovarian cancer |

## Oncoviruses

**Viruses which cause cancer**

- These may be detected on blood test and prevented by vaccine

These are the main types of oncoviruses and their diseases:

| Oncovirus | Cancer |
|---|---|
| Epstein-Barr virus | Burkitt's lymphoma<br>Hodgkin's lymphoma<br>Post transplant lymphoma<br>Nasopharyngeal carcinoma |
| Human papillomavirus 16/18 | Cervical cancer<br>Anal cancer<br>Penile cancer<br>Vulval cancer<br>Oropharyngeal cancer |
| Human herpes virus 8 | Kaposi's sarcoma |
| Hepatitis B virus | Hepatocellular carcinoma |
| Hepatitis C virus | Hepatocellular carcinoma |
| Human T-lymphotropic virus 1 | Tropical spastic paraparesis<br>Adult T cell leukaemia |

## Membrane receptors

**There are four main types of membrane receptor:**

1) Ligand-gated ion channels.
2) Tyrosine kinase receptors.
3) Guanylate cyclase receptors.
4) G protein-coupled receptors.

### 1) Ligand-gated ion channel receptors:

- Generally mediate fast responses
- E.g. **nicotinic acetylcholine**, GABA-A & GABA-C, glutamate receptors.

### 2) Tyrosine kinase receptors:

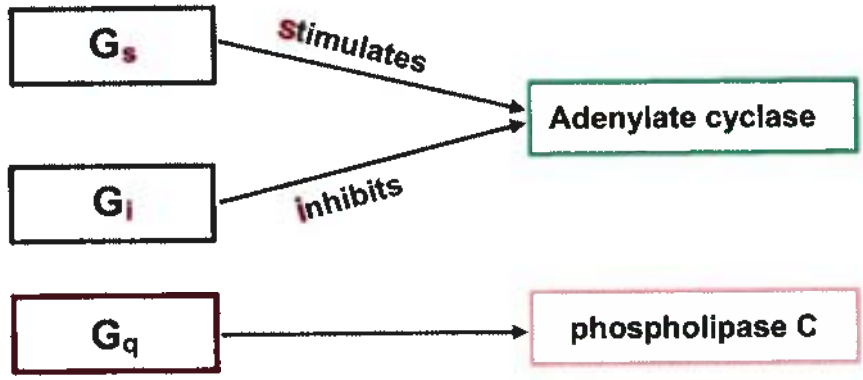
- Intrinsic tyrosine kinase: **insulin**, insulin-like growth factor (IGF), epidermal growth factor (EGF).
- Receptor-associated tyrosine kinase: GH, prolactin, IFN, interleukin.

### 3) Guanylate cyclase receptors:

- Contain intrinsic enzyme activity
- E.g. atrial natriuretic factor (**ANF**), brain natriuretic peptide (**BNP**) and nitric oxide (**NO**).

### 4) G protein-coupled receptors:

- G protein-coupled receptors **span the cell membrane.**
- Generally mediate slow transmission and affect metabolic processes.
- Activated by a wide variety of extracellular signals e.g. Peptide hormones, biogenic amines, lipophilic hormones, light.
- 7-helix membrane-spanning domains.
- Consist of 3 main subunits: alpha, beta and gamma.
- The alpha subunit is linked to GDP.Ligand binding causes conformational changes to receptor, GDP is phosphorylated to GTP, and the alpha subunit is activated.
- G proteins are named according to the alpha subunit ($G_s$, $G_i$, $G_q$).
- e.g. **Adenosine**, muscarinic acetylcholine, **adrenergic receptors**, GABA-B, growth hormone.



| | $G_s$ | $G_i$ | $G_q$ |
|---|---|---|---|
| **Mechanism** | Activates adenylate cyclase → increases cAMP → activates protein kinase A | Inhibits adenylate cyclase → decreases cAMP → inhibits protein kinase A | Activates phospholipase C → splits $PIP_2$ to $IP_3$ & DAG → activates protein kinase C |
| **Examples** | • Beta-1 receptors (epinephrine, norepinephrine, dobutamine).<br>• Beta-2 receptors (epinephrine, salbuterol).<br>• H2 receptors (histamine).<br>• D1 receptors (dopamine).<br>• V2 receptors (vasopressin).<br>• Receptors for ACTH, LH, FSH, glucagon, PTH, calcitonin, prostaglandins. | • **M2** receptors (**acetylcholine**).<br>• Alpha-2 receptors (epinephrine, norepinephrine).<br>• D2 receptors (dopamine).<br>• GABA-B receptor. | • Alpha-1 receptors (epinephrine, norepinephrine).<br>• H1 receptors (histamine).<br>• V1 receptors (vasopressin).<br>• M1, M3 receptors (acetylcholine). |

**Nicotinic** Ach receptors >>>> **Ligand-gated ion channel receptors.**
**Muscarinic** Ach receptors >>> **G- protein coupled receptors.**

## Autosomal dominant conditions

Kindly note that: Autosomal **recessive** conditions are often thought to be **'metabolic'** as opposed to autosomal **dominant** conditions being **'structural'**, notable exceptions:

- Some 'metabolic' conditions such as Hunter's and G6PD are X-linked recessive, whilst others such as hyperlipidaemia type II and hypokalaemic periodic paralysis are autosomal dominant.
- Some 'structural' conditions such as ataxia telangiectasia and Friedreich's ataxia are autosomal recessive.

- **Autosomal dominant** conditions are **'structural'** - exceptions: hyperlipidaemia type II, hypokalaemic periodic paralysis.
- **Autosomal recessive** conditions are **'metabolic'** - exceptions: inherited Friedreich's ataxias, ataxia telangiectasia.

## In autosomal dominant diseases:

- **Both homozygotes** and **heterozygotes manifest disease** (there is **no carrier state)**
- **Both males** and **females** affected
- Only affected individuals can pass on disease
- Disease is **passed on to 50% of children**
- Normally appears in every generation (although see below)
- **Risk remains same for each successive pregnancy**

## Complicating factors:

- **Non-penetrance**: (i.e. **affected individuals do not always have affected parents)** lack of clinical signs and symptoms (normal phenotype) despite abnormal gene. E.g. 40% otosclerosis
- Spontaneous mutation: new mutation in one of gametes e.g. 80% of individuals with achondroplasia have unaffected parents

**The following conditions are autosomal dominant:**

1) Achondroplasia
2) Acute intermittent porphyria
3) **Adult polycystic disease**
4) Antithrombin III deficiency
5) Ehlers-Danlos syndrome
6) Familial adenomatous polyposis (**FAP**)
7) Hereditary haemorrhagic telangiectasia
8) Hereditary spherocytosis
9) Hereditary non-polyposis colorectal carcinoma
10) **Huntington's** disease
11) Hyperlipidaemia type II
12) Hypokalaemic periodic paralysis
13) Malignant hyperthermia
14) **Marfan's syndromes**
15) **Myotonic dystrophy**
16) Neurofibromatosis
17) **Noonan syndrome**
18) Osteogenesis imperfecta
19) Peutz-Jeghers syndrome
20) **Retinoblastoma**
21) Romano-Ward syndrome
22) **Tuberose sclerosis**
23) Von Hippel-Lindau syndrome
24) **Von Willebrand's disease.**

Type 3 von Willebrand's disease (most severe form) is inherited as an autosomal recessive trait. Around 80% of patients have type 1 disease

# Osteogenesis imperfecta ("brittle bone disease")

## Pathophysiology

- **Autosomal dominant mutation in COL1A1 or COL1A2 genes** >>↓ synthesis of normal type I collagen >> impaired bone matrix formation (osteogenesis)

## Features

- **Growth retardation**
- **Skeletal deformities, brittle bones, and recurrent fractures from minimal trauma**
- **Blue sclerae due to visible choroidal pigment.**
- **Progressive hearing loss** secondary to **otosclerosis**
- **Brittle, opalescent teeth** (dental imperfections) due to a lack of dentin formation.

## Types

- **type 1:** the most common, and milder form.
- **Type II**: most severe form; lethal perinatally or within the first year

## Diagnosis

- DNA test
- Ultrasonography before birth and radiographic skeletal survey afterwards (fractures, callus, deformities)
- **Bone or skin biopsy >> type 1 collagen mutation**

## Treatment

- No cure available
- Bisphosphonates; decrease the risk of fractures
- Surgery for functional improvement

Individuals with osteogenesis imperfecta can't BITE: Bones (recurrent fractures), I ("eye" = blue sclerae, Teeth dental abnormalities, Ears hearin loss.

**MRCPUK part 1 exam: A pregnant woman is known to have polycystic kidney disease. What is the chance her child will also have the disease?** >> 50% (Polycystic kidney disease is usually inherited in an autosomal dominant fashion and hence 50% of her children will be affected, regardless of gender)

# Achondroplasia

Achondroplasia an **autosomal dominant** condition and one of the commonest forms of short-limbed dwarfism.

It is caused by an activated point-mutation of the fibroblast growth factor receptor 3 (at 4p16.3).

The incidence increases **with paternal age**.

**Epiphyseal growth cartilage fails**, but there is **normal bone formation** and **repair**. There is therefore **no increased risk of fracture**. The homozygous form is usually fatal.

- short limbs (rhizomelia) with shortened fingers (brachydactyly)
- large head with frontal bossing and narrow foramen magnum
- midface hypoplasia with a flattened nasal bridge
- 'trident' hands
- lumbar lordosis

**Subfertility** is **NOT** associated with achondroplasia.

## Treatment

There is no specific therapy. However, some individuals benefit from limb lengthening procedures. These usually involve application of Ilizarov frames and targeted bone fractures. A clearly defined need and end point is the cornerstone of achieving success with such procedures.

- **medical**
  - Early administration of **growth hormone** (1–6 years)
- **Surgical corrections:**
  - spinal stenosis, secondary scoliosis, genu varum, foramen magnum decompression

# Marfan's syndrome

Marfan's syndrome is caused by a mutation in a protein called fibrillin-1

## Overview

- **autosomal dominant** connective tissue disorder.
- caused by a defect in the fibrillin-1 gene on chromosome **15**
- Mutation of **FBN1** that encodes **Fibrillin-1.**
- affects around 1 in 3,000 people.
- may occur as a spontaneous mutation, (1/3rd of cases), and this occurs more commonly to offspring of older males.

## Features

### Skeletal

- tall stature with arm span to height ratio > 1.05
- high-arched palate
- arachnodactyly
- pectus excavatum
- pes planus
- scoliosis of > 20 degrees
- crowded teeth.
- Dural ectasia:
  - ballooning of the dural sac at the lumbosacral level
  - Dural ectasia affects around 60% of patients with Marfan's syndrome.
  - **It may cause lower back pain associated with neurological problems such as bladder and bowel dysfunction.**
- ligamentous/joint laxity resulting in multiple joint dislocations, hypermobile joints

**Heart:** **dilation of the aortic sinuses (seen in 90%)** which may lead to aortic aneurysm, aortic dissection, aortic regurgitation, mitral valve prolapse (75%),

**lungs:** repeated pneumothoraces

**eyes:**

- **upwards** lens dislocation (superotemporal ectopia lentis) seen in 50% of patients,
- **Retinal detachment**
- blue sclera, myopia early glaucoma, and early cataracts.

## Diagnosis

- Unfortunately, **DNA testing for fibrillin gene mutations, whilst helpful, cannot exclude a diagnosis of Marfan because a number of mutations exist (at least 130)**.
- Hence **diagnosis is made on the major and minor features associated with the syndrome.**

## Prognosis & treatment:

- The life expectancy of patients used to be around 40-50 years.
- With the advent of regular echocardiography monitoring and beta-blocker/ACE-inhibitor therapy this has improved significantly over recent years.
  - Treatment with **β-blockers** reduces the rate of aortic dilatation and the risk of rupture
- Aortic dissection and other cardiovascular problems remain the leading cause of death however.
- Pregnancy is associated with increased risk of aortic rupture.

**A mutation of which gene is most closely associated with Marfan's syndrome?**

**>> FBN-1 mutation**

- FBN-1 gene mutation >> Defect in fibrillin >> Marfan's

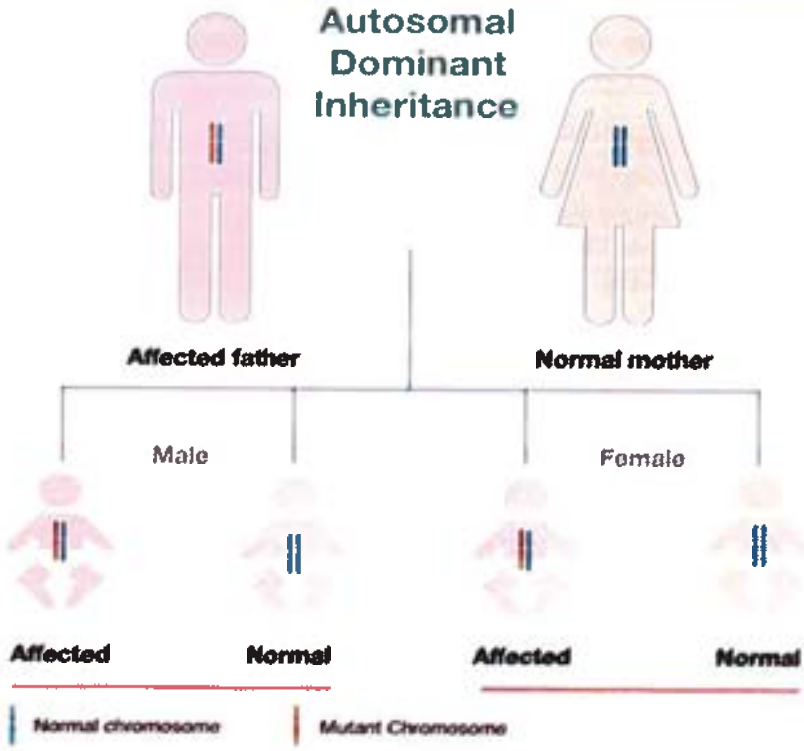
# Noonan's syndrome

Often thought of as the **'male Turner's'**, Noonan's syndrome is an **autosomal dominant** condition associated with **a normal karyotype**.

It is thought to be caused by a defect in a gene on chromosome **12**.

As well as features similar to Turner's syndrome (webbed neck, widely-spaced nipples, short stature, pectus carinatum and excavatum), a number of characteristic clinical signs may also be seen:

- Cardiac: **pulmonary valve stenosis**
- **Ptosis**
- **Triangular-shaped face**
- **Low-set ears**
- Coagulation problems: **factor XI deficiency**




The inheritance pattern of autosomal dominant inheritance

## Autosomal recessive conditions

### In autosomal recessive inheritance:

- **Only homozygotes** are affected
- Males and females are **equally likely** to be affected
- Not manifest in every generation - may **'skip a generation'**

### If one affected parent (i.e. homozygote for gene) and one unaffected (i.e. not a carrier or affected):

- **ALL** the children will be **carriers.**

### If two heterozygote parents:

- **25%** chance of having an affected (homozygote) child
- **50%** chance of having a carrier (heterozygote) child
- **25%** chance of having an unaffected (i.e. genotypical) child

**Autosomal recessive disorders** are **often metabolic** in nature and are generally **more life-threatening compared to autosomal dominant** conditions.

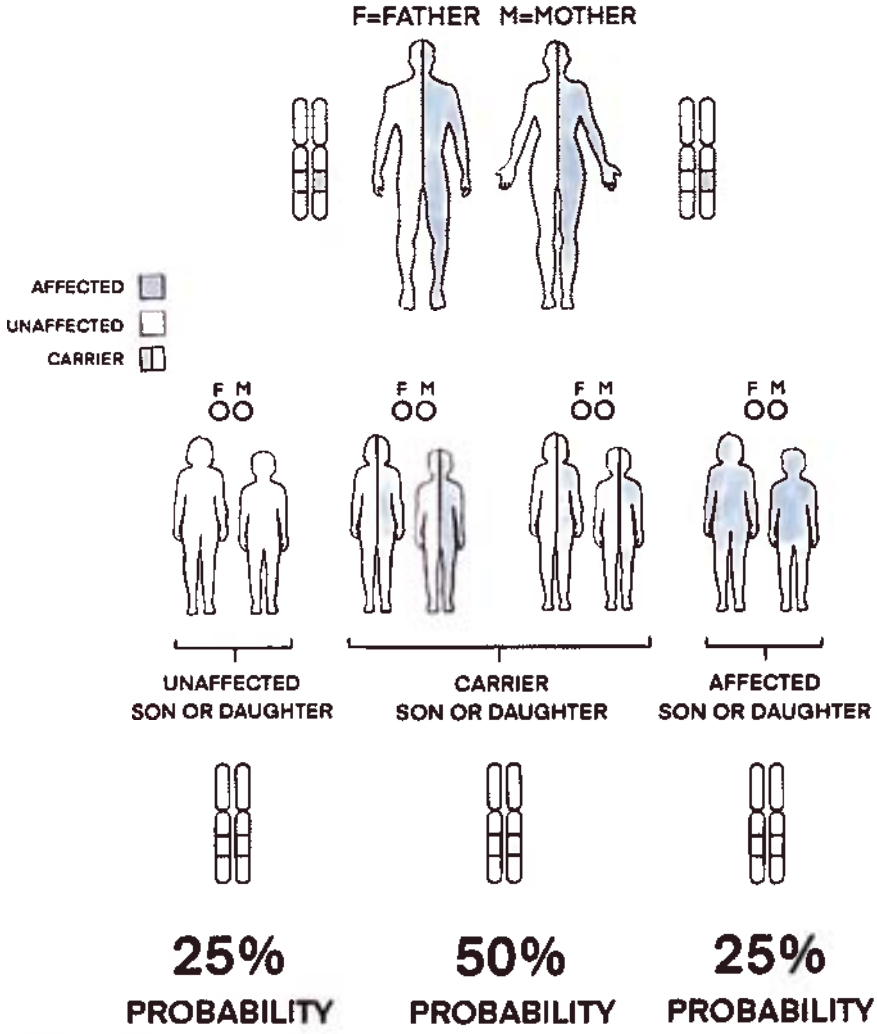
## The following conditions are autosomal recessive:

- **Albinism**
- **Ataxia telangiectasia**
- **Congenital adrenal hyperplasia**
- **Cystic fibrosis**
- Cystinuria
- Familial Mediterranean Fever
- Fanconi anaemia
- **Friedreich's ataxia**
- **Gilbert's** syndrome: this is still a matter of debate and many textbooks will list Gilbert's as autosomal dominant.
- Glycogen storage disease
- Haemochromatosis
- Homocystinuria
- Lipid storage disease: Tay-Sach's, Gaucher, Niemann-Pick
- Mucopolysaccharidoses: Hurler's
- PKU
- **Sickle cell anaemia**
- **Thalassaemias**
- **Wilson's** disease

As cystic fibrosis is an autosomal recessive condition there is a **50%** chance that their next child will be a **carrier** of cystic fibrosis (i.e. be heterozygous for the genetic defect) and a **25%** chance that the child will **actually have** the disease (be homozygous) and **25%** chance to be **free**.

## Autosomal recessive

### BOTH PARENTS ARE CARRIERS




**MRCPUK part 1 exam: A man diagnosed as having hereditary hemochromatosis. His wife is not a carrier. What is the chance his child will develop haemochromatosis?** **>> 0%** (Haemochromatosis is an autosomal recessive condition. If one of the parents has haemochromatosis (i.e. is homozygous) and the other is not a carrier/affected, then all the children will inherit one copy of the gene from the affected parent and hence will be carriers)

## Galactosaemia

Galactosaemia is a rare autosomal recessive condition caused by the **absence** of **galactose-1-phosphate uridyl transferase**. This results in intracellular accumulation of galactose-1-phosphate.

**Features:**

- **Jaundice**
- **Failure to thrive**
- **Hepatomegaly**
- **Cataracts**
- **Fanconi syndrome**
- **Hypoglycaemia** after exposure to galactose

**Diagnosis:** Urine reducing substances

**Management** is with a galactose free diet

## Pseudoxanthoma elasticum

Pseudoxanthoma elasticum is an inherited condition (usually autosomal recessive) characterised by an abnormality in **elastic fibres**.

Also there are reports of autosomal dominant inheritance in a minority of cases.

**Features:**

- **Retinal angioid streaks.**
- **'Plucked chicken skin'** appearance - small yellow papules on the neck, antecubital fossa and axillae.
- **Cardiac**: **mitral valve prolapse**, increased risk of **IHD**.
- **GI haemorrhage.**

## Gaucher's disease

**Pathophysiology**

Autosomal recessive mutation in the glucocerebrosidase (GBA) gene located on chromosome 1 >> Deficiency of (3-glucocerebrosidase-+ accumulation of glucocerebroside (sphingolipid found in cell membranes that can accumulate in the lysosome of macrophages) in the brain, liver, spleen, and bone marrow (i.e., Gaucher cells).

**Epidemiology**

- Gaucher's disease is the most common lysosomal storage diseases.
- About one in 100 people in the United States are carriers of the most common type of Gaucher disease (type I).

- The carrier rate among Ashkenazi Jews is 8.9% while the birth incidence is one in 450.

## Consequences

- **Parkinson's disease is more common in Gaucher's disease patients** (the most common known genetic risk factor for Parkinson's)
- Cancer risk may be increased, particularly myeloma

## Types

**GD type I** (Chronic **non-neuropathic**; adult Gaucher disease)

- **most common form**
- associated with a normal lifespan

**GD type II** (Acute neuropathic; infantile Gaucher disease)

- typically begins within 6 months of birth
- Symptoms include, progressive brain damage, spasticity, seizures
- carries the worst prognosis, affected children **usually die by age two.**

**GD type III** (**Subacute neuropathic**; juvenile Gaucher disease)

- can begin at any time in childhood or even in adulthood,
- characterized by slowly progressive, but milder **neurologic symptoms** compared to type II.
- **Patients often live into their early teen years and adulthood**

## Features

- Hepatosplenomegaly
- Bone pathology (bone crises, osteoporosis, aseptic necrosis) **the chief complaint is of bone pain in an adult.**
- Blood abnormalities: anemia, thrombocytopenia
- diffuse infiltrative pulmonary disease
- Growth delays
- Yellowish-brown skin and scleral pigmentation: **Characteristic yellow or yellow-brown papules (pingueculae) develop at the sclerocorneal junctions.**

## Investigations

- **enzyme analysis (Enzyme studies of blood leucocytes) >> Reduced** glucocerebrosidase activity in leukocytes or fibroblasts
- Accumulation of glucocerebrosidase in fibroblasts or leukocytes (Gaucher cells)
- **Gaucher cell: lipid-rich macrophages with an enlarged cytoplasm with inclusions that resemble crumpled tissue paper on microscopy**

**Treatment:** recombinant glucocerebrosidase.

# Homocystinuria

Homocystinuria is a rare autosomal recessive disease caused by a **deficiency of cystathionine beta synthase**.

This results in severe elevations in plasma and urine homocysteine concentrations.

## Features

- often patients have fine, fair hair
- musculoskeletal
  - Marfanoid body habitus: arachnodactyly etc
  - osteoporosis
  - kyphosis
- neurological: may have learning difficulties, seizures
- ocular
  - **downwards (inferonasal) dislocation of lens**
  - severe myopia
- **increased risk of arterial and venous thromboembolism**
- also malar flush, livedo reticularis

## Investigations

- increased homocysteine levels in serum and urine
- cyanide-nitroprusside test: also positive in cystinuria

**Treatment is vitamin B6 (pyridoxine)** supplements.

## Homocystinuria VS Marfan's

| | homocystinuria | Marfan's syndrome |
|---|---|---|
| **Inheritance** | Autosomal **recessive** | Autosomal **dominant** |
| **lens dislocation** | **downward** lens dislocation | **upward** lens dislocation |
| **aortic incompetence** | heart rarely affected | aortic incompetence may occur |
| **intellectual development** | **mental retardation** (nearly 50%) | **normal** |
| livedo reticularis | **seen** due to the venous thrombosis in the small vessels of the skin | **NO** |
| **other principle features** | **osteoporosis**, recurrent thromboembolism; **characteristic laboratory features**: plasma methionine and homocystine levels are elevated, homocystine is excreted in the urine, plasma cystine levels are reduced, positive urine cyanide-nitroprusside test; response to treatment with pyridoxine | flat feet, herniae, scoliosis; there is a 50% reduction in life expectancy |

## X-linked recessive

- In X-linked recessive inheritance **only males are affected**.
- An **exception** to this seen in examinations are **patients (females) with Turner's syndrome, who are affected due to only having one X chromosome.**
- X-linked recessive disorders are **transmitted by heterozygote females (carriers)** and **NO male-to-male transmission**.
- Males will pass on the **'bad' X chromosome** to their **daughters** so that they become **carriers**, they are **not** usually affected as they will have a 'good' X from the normal mothers, **Males** pass on their **Y** chromosomes to any sons, therefore they will **not** be affected.
- So male with G6PD + Normal female >>>> All children will not be affected, but the daughters will be carrier to be affect the incoming their boys.
- **Affected males can have unaffected sons and carrier daughters.**
- As **his sons** will get the X chromosome from his wife and so will not be carriers but all **his daughters** will be carriers.

X-linked recessive conditions >>> there is **no male-to-male transmission**. **Affected males** can only have **unaffected sons** and **carrier daughters**.

And one of **his relatives** is most likely to have the condition is >> **his Mother's father**

His daughters' sons will consequently have a 50% chance of inheriting the disease as **all his daughters are carriers** and there is a **1 in 2 chance (50:50)** of **passing the gene on to their sons.**

Haemophilia is an X-linked recessive disorder and would hence be expected **only** to occur in **males**. With exception that only appears in **female** patient if with **Turner's** syndrome **only have one X chromosome** however, they may develop X-linked recessive conditions.

A 14-year-old **girl** presents with a swollen left knee. She suffers from **haemophilia** and has been treated for a right-sided haemarthrosis previously. What other condition is she most likely to have >> **Turner's syndrome**.

Each **male** child of a heterozygous female carrier has a **50% chance of being affected** whilst each **female** child of a heterozygous female carrier has **a 50% chance of being a carrier.**

The possibility of an affected father having children with a heterozygous female carrier is generally speaking extremely rare. However, in certain Afro-Caribbean communities G6PD deficiency is relatively common and homozygous females with clinical manifestations of the enzyme defect are seen.

## The following conditions are inherited in an X-linked recessive fashion:

- **Androgen insensitivity syndrome**
- **Becker** muscular dystrophy
- **Duchenne** muscular dystrophy
- **Fabry's disease**
- **G6PD deficiency**
- **Haemophilia A,B**
- Hunter's disease
- Lesch-Nyhan syndrome
- Nephrogenic diabetes insipidus
- **Colour blindness**

- **Ocular albinism**
- **Retinitis pigmentosa**
- **Wiskott-Aldrich syndrome (WAS)**
- Chronic granulomatous disease: it has varying patterns of inheritance, with the majority being in an X-linked recessive fashion (in > 70%).

## Fabry disease

### Overview

- **X-linked recessive**
- deficiency of alpha-galactosidase A

### Features

- burning pain/paraesthesia in childhood
- angiokeratomas
- lens opacities
- proteinuria
- early cardiovascular disease

### Diagnosis

- **absent or deficient levels of alpha-galactosidase A** in leucocytes, plasma or cultured fibroblasts.
- The gold standard for the diagnosis of Fabry disease is **gene analysis of alpha-galactosidase A (GLA) gene.**
- **slit-lamp examination** of the cornea, which reveals microscopic lipid deposits
- Microscopy of the spun urine sediment may demonstrate 'Maltese cross' lipid globules

**In Fabry disease, tissue accumulation of which is most likely to occur?** **>> Trihexosyl ceramide**

**Treatment:** enzyme replacement

# Kallman's syndrome

Kallman's syndrome is a recognised cause of delayed puberty secondary to **hypogonadotropic hypogonadism**.

It is usually inherited as an **X-linked recessive** trait.

Incidence of 1 in 10,000 male.

Kallman's syndrome is thought to be caused by **failure of GnRH-secreting neurons and the olfactory neurones to migrate to the hypothalamus during development.**

The clue given in many questions is **lack of smell (anosmia)** (in **75%** of cases) in a **boy** with **delayed puberty** and an increased association with **cleft lip and palate**.

Kallman's syndrome may arise due to abnormalities of the KAL-1 or KAL-2 gene (encoding anosmin-1 and FGF-1).

Whilst the majority of cases are sporadic, perhaps up to 50% of cases are due to genetic inheritance.

**Fluorescent in situ hybridisation** (**FISH**), using a specific chromosomal probe, is currently **the best means** of a genetic diagnosis of this condition.

**MRI brain**: **Absent olfactory bulbs** in **75%** of MRI scans.

## Features:

- **'Delayed puberty'**
- **Hypogonadism**: **cryptorchidism (undescended testes) in males or primary amenorrhoea in female**
- **Anosmia**
- Sex hormone (Oestrogen in female or Testosterone in male) are **low.**
- LH, FSH levels are **inappropriately low/normal**, (rather than the high concentrations expected with primary gonadal failure).
- Otherwise normal anterior pituitary function (**Normal prolactin**).
- Patients are typically of normal or above average height.
- Cleft lip/palate and visual/ sensorineural hearing defects are also seen in some patients

### Treatment:

- **Pulsed GnRH therapy** or **gonadotrophin** therapy can be used to restore fertility, or
- **Testosterone** can be used to drive development and restore of secondary sexual characteristics, but won't restore fertility.

**EX**: A 16-year-old male has lack of pubertal development + his testes are undescended and there is only scanty pubic hair. The most likely diagnosis is **Kallman's syndrome.**

**Klinefelter's** >>> LH & FSH **raised**
**Kallman's** >>> LH & FSH **low-normal, at least not raised**

**NB**: **Andropause** is the term for the gradual decrease in serum testosterone concentration with age, but does not occur, usually, until after the age of 50.

With men, gonadal failure occurs typically more slowly than in women at the menopause. Thus a 50-year-old man would not necessarily be expected to show a picture of gonadal failure.

In **ageing** and **primary testicular failure** >>> **LH and FSH are elevated** and **testosterone is low**.
In **hypopituitarism** >>> all are low (Low LH, FSH and Testosterone).
Many men are treated with **gonadotrophin antagonists** (as in cancer prostate) can cause a similar pattern to hypopituitarism.
**NB:** in **haemochromatosis** also >>> pituitary infiltration >>> Hypo gonadotrophic hypogonadism (all are low) >>> so check serum **ferritin**.

## X-linked dominant

### The following conditions are inherited in an X-linked dominant fashion:

- **Alport's syndrome** (see nephrology) :( in around 85% of cases - 10-15% of cases are inherited in an autosomal recessive fashion with rare autosomal dominant variants existing).
- **Vitamin D resistant rickets.**
- **Rett syndrome.**

**NB**: Pseudohypoparathyroidism was previously classified as an X-linked dominant condition but has now been shown to be inherited in an autosomal dominant fashion in the majority of cases.

# Trinucleotide repeat disorders

Trinucleotide repeat disorders are genetic conditions caused by an abnormal number of repeats (expansions) of a repetitive sequence of three nucleotides.

These expansions are unstable and may enlarge which may lead to **an earlier age of onset in successive generations** - a phenomenon known as "**anticipation**".

In **most** cases, an **increase in the severity of symptoms is also noted**.

The 'classic' definition of anticipation is earlier onset in successive generations. However, in most cases, an increase in the severity of symptoms is also noted. If both options are presented then the second one should be chosen, as this represents the more accepted definition of anticipation.

**"Anticipation"** in trinucleotide repeat disorders = **earlier onset in successive generations.**

## Examples: (Note dominance of neurological disorders):

- **Fragile X** (CGG)
- **Huntington's (CAG)**
- **Motonic dystrophy** (CTG)
- **Friedreich's** ataxia (GAA): it is unusual in not demonstrating anticipation
- Spinocerebellar ataxia
- Spinobulbar muscular atrophy
- **Kennedy disease,** also known as 'X-linked bulbospinal neuronopathy'
- Dentatorubral pallidoluysian atrophy

**Trinucleotide repeat disorders mnemonic:**
**Try (trinucleotide) hunting for my fried eggs (X).**

## Fragile X

Fragile X is a **trinucleotide repeat** disorder.

**Features in males:**

- **Mental retardation** and **Learning difficulties**
- **Large low set ears**, long thin face, high arched palate
- **Macroorchidism**
- **Hypotonia**
- **Autism** is more common
- **Mitral valve prolapse**

**Features in females** (who have one fragile chromosome and one normal X chromosome) range from normal to mild.

**Diagnosis:** Can be made antenatally by **chorionic villus** sampling or amniocentesis

Analysis of the number of **CGG** repeats using restriction endonuclease digestion and **Southern** blot analysis

## Imprinting

**Definition:** **imprinting** is a phenomenon by which certain genes are expressed in a parent-of-origin-specific manner.

- **the term 'imprinting' refers to >> Differential expression of alleles contingent on their parental origin**
  - If the allele inherited from the father is imprinted, it is thereby silenced, and only the allele from the mother is expressed.
  - If the allele from the mother is imprinted, then only the allele from the father is expressed.

**Mechanism**

- poorly understood but does **involve DNA methylation**.
- Disease may occur as a result of a defect in one allele if the other allele is imprinted and hence not expressed.

**Examples**

diseases involving genomic imprinting include:

- Prader–Willi syndrome (paternally imprinted)
- Angelman syndrome (maternally imprinted)

# Prader-Willi syndrome

It is an example of genetic imprinting where the **phenotype depends** on whether the **deletion** occurs on a gene inherited from the mother or father:

- **Prader-Willi syndrome** if gene deleted from **father**
- **Angelman syndrome** if gene deleted from **mother**

**Deletion of chromosome 15:**
- Prader-Willi - paternal
- Angelman syndrome – maternal

Prader-Willi syndrome is associated with the absence of the active Prader-Willi gene on the long arm of chromosome **15**. This may be due to:

- **Microdeletion** of **paternal 15q11-13** (**70%** of cases).
- Maternal uniparental disomy of chromosome 15.

The most common genetic cause is >> **Microdeletion** of the **paternal 15q11-13**

## Features:

- Hypotonia during infancy
- Dysmorphic features
- Short stature
- Hypogonadism and infertility
- Learning difficulties
- Childhood obesity
- Behavioural problems in adolescence

## Treatment

- **administration of growth hormone and sex hormones (testosterone) is the treatment of choice**
- **Calorie restriction**

**MRCPUK part 1e xam: Which one of the following is the most common genetic cause of Prader-Willi syndrome?**
**>> Microdeletion of the paternal 15q11-13**

**Chromosome 15 is implicated in Prader-Willi, Angelman, and Marfan syndromes.**

# Mutations

## Missense mutation

- substitution in one amino acid in a protein
- e.g: glutamic acid is substituted by valine in **sickle-cell disease**

## nonsense mutation

- the altered DNA sequence prematurely signals the cell to stop building a protein. This type of mutation results in a shortened protein that may function improperly or not at all.

## insertion mutation

- changes the number of DNA bases in a gene by **adding a piece of DNA**. As a result, the protein made by the gene may not function properly.

## Frameshift mutation

- insertions or deletions of nucleotides
- e.g: cystic fibrosis

## Point mutation

- a change in a single nucleotide
- e.g: C282Y mutation responsible for haemochromatosis

## Splicing mutation

- results in larger nonfunctional protein
- e.g: β-thalassemia

## Large Segment Deletion

- Unequal crossover at meiosis results in loss of large segment of DNA
- Loss of function mutation
- e.g., α-thalassemia (deletion of α-globin gene)

## Termination mutation

- generation of a premature stop codon
- e.g: Hurler syndrome

## Polygenic diseases

**Definition:**

- genetic disorder that is caused by the **combined action of more than one gene**.
- Because such disorders depend on the presence of several genes, they are not inherited as simply as are single-gene diseases.

**Examples:**

- hypertension,
- coronary heart disease,
- diabetes
- **Amyotrophic lateral sclerosis (ALS)**

## Second messengers

**Overview:**

- Many different types
- Allow amplification of external stimulus

| | cAMP system | Phosphoinositol system | cGMP system | Tyrosine kinase system |
|---|---|---|---|---|
| **Ligand: Neurotransmitters (Receptor)** | Epinephrine (α2, β1, β2) Acetylcholine (M2) | Epinephrine (α1) Acetylcholine (M1, M3) | - | - |
| **Ligand: Hormones** | ACTH, ADH, calcitonin, FSH, glucagon, hCG, LH, MSH, PTH, TSH, GHRH* | angiotensin II, GnRH, GHRH*, Oxytocin, TRH | **ANP, Nitric oxide (NO)** | **Insulin, growth hormone (GH)**, IGF, PDGF |
| **Primary effector** | Adenylyl cyclase | Phospholipase C | Guanylate cyclase | Receptor tyrosine kinase |
| **Secondary messenger** | cAMP (cyclic adenosine monophosphate) | IP3 (inositol 1,4,5 trisphosphate) and DAG (Diacylglycerol) | cGMP | Protein phosphatase |

In **GHRH** and **Adrenaline** >> the **cAMP** pathway is the most important.

# Lysosomal storage diseases

## Definition

- Lysosomal storage diseases are a group of inherited metabolic disorders caused by a deficiency of specific enzymes. This causes an accumulation of abnormal substances that are usually degraded within lysosomes, resulting in cell damage and death.

## Risk factors

- Ashkenazi ethnicity
- Male sex

# Mucopolysaccharidoses (Hurler's & Hunter's syndrome)

## Pathophysiology

Mutations in lysosomal enzymes >> impaired breakdown of glycosaminoglycans >> Accumulation of glycosaminoglycans, i.e., heparan sulfate (HS) and dermatan sulfate (OS)

## Features

**Occur in both conditions (typically milder in Hunter syndrome):**

- Developmental delay
- Facial dysmorphism: frontal bossing, elongated skull , flattened nasal bridge, broad nasal tip, thickened gingiva, anteverted nostrils, constant nasal discharge, spaced and protruded eyes.
- Airway obstruction
- Hepatosplenomegaly

## Diagnosis

- Increased urinary levels of dermatan sulfate (OS) and heparan sulfate (HS)
- Enzyme assay to confirm specific enzyme deficiency (definitive test)

## Treatment

- Enzyme replacement therapy
- Bone marrow transplantation

| | Hurler syndrome (mucopolysaccharidosis type I) | Hunter syndrome (mucopolysaccharidosis type II) |
|---|---|---|
| **Inheritance** | Autosomal recessive | X-linked recessive |
| **Pathophysiology** | Deficiency of a-L iduronidase (enzyme responsible for the hydrolysis of glycosaminoglycans) | Deficiency of iduronate-2-sulfatase |
| **Features** | ➢ Corneal clouding<br>➢ Inguinal hernia | ➢ Aggressive behavior, Hyperactivity<br>➢ No corneal clouding<br>➢ Carpal tunnel syndrome |

**Which feature suggests a diagnosis of Hurler's syndrome rather than Hunter's syndrome?** **>> Cloudy cornea.**

**Hunter syndrome presents as Hurler syndrome, but patients with Hunter syndrome have normal vision and aggressive behavior.**

## Collagen synthesis and disorders

**Types of collagen**

| | Tissue distribution | Related conditions |
|---|---|---|
| **Type I collagen (90% of body collac:ien)** | Bone (produced by osteoblasts), skin, tendons, ligaments, fascia, dentin, cornea, internal organs, scartissue (late stages of wound healing) | Osteogenesis imperfectatype I: decreased production |
| **Type II collagen** | Cartilage (including hyaline), vitreous humor of the eye, intervertebral discs (nucleus pulposus) | Achondrogenesis (type II) |
| **Type III collagen (reticulin)** | Reticular fibers in skin, blood vessels, granulation tissue, uterus, scar tissue (early stages of wound healing), fetaltissue in early embryos and throuqhout embryoqenesis | Ehlers-Danlos syndrome (vascular type): decreased production |
| **Type IV collagen** | Basement membranes, lens | Alport syndrome: decreased production Goodpasture syndrome: autoantibodies target type IV collagen |
| **Type V collagen** | Bone, skin, fetal tissue, placenta | Ehlers-Danlos syndrome (classic type) |

## Structure

- Composed of 3 polypeptide strands that are woven into a helix, usually a combination of glycine with either proline or hydroxyproline plus another amino acid
- Numerous hydrogen bonds exist within molecule to provide additional strength
- Many subtypes but commonest subtype is I (90% of bodily collagen), tissues with increased levels of flexibility have increased levels of type III collagen
- Vitamin C is important in establishing cross-links
- Synthesised by fibroblasts

## Collagen diseases

Disorders of collagen range from relatively common, acquired defects (typically aging), through to rarer congenital disorders. The latter are exemplified by conditions such as osteogenesis imperfecta and Ehlers Danlos syndromes.

### Osteogenesis imperfecta:

- 8 Subtypes
- Defect of type I collagen
- In type I the collagen is normal quality but insufficient quantity
- Type II- poor quantity and quality
- Type III- Collagen poorly formed, normal quantity
- Type IV- Sufficient quantity but poor quality
- Patients have bones which fracture easily, loose joint and multiple other defects depending upon which sub type they suffer from.

### Ehlers Danlos:

- Multiple sub types
- Abnormality of types 1 and 3 collagen
- Patients have features of hypermobility.
- Individuals are prone to joint dislocations and pelvic organ prolapse. In addition to many other diseases related to connective tissue defects.

In paediatric practice medulloblastomas (neuroectodermal tumours) were the commonest lesions, astrocytomas now account for the majority.
Tumours arising in right temporal and frontal lobe may reach considerable size before becoming symptomatic.
Whereas tumours in the speech and visual areas will typically produce early symptoms.

**Diagnosis**: MRI Scanning provides the best resolution.
**Treatment**: Usually surgery, even if tumour cannot be completely resected conditions such as rising ICP can be addressed with tumour debulking and survival and quality of life prolonged.
Curative surgery can usually be undertaken with lesions such as meningiomas. Gliomas have a marked propensity to invade normal brain and resection of these lesions is nearly always incomplete

## Glycogen storage disorders (GSD)

### Key feature of glycogen storage disorders:

- Tay-Sachs commonly has a 'cherry red spot' macula
- Pompe disease leads to cardiomyopathies
- McArdle's disease leads to rhabdomyolysis after exercise and lactic acidaemia
- Von Gierke disease leads to hypoglycaemia and hepatomegaly

### Pompe trashes the Pump (heart)

#### Glycogen

- Glycogen is the storage form of carbohydrate, found predominantly in muscle and liver.
- **Chains of glucose residues are linked by alpha-1,4 glycosidic bonds, i.e. between the first carbon of one glucose and the fourth carbon of the next. Branches occur about every ten residues, and are formed by alpha-1,6 glycosidic linkages.**
- Glycogen synthesis and degradation occur at the tips of branches, with the branching structure increasing the number of sites at which glucose residues can be added or removed.

**Pompe's disease** or acid maltase deficiency **(glycogen storage disorder type 2): is a deficiency in alpha-glucosidase.** It produces a myopathy, restrictive cardiomyopathy and hepatomegaly.

**Glycogen storage disorders:**

- **Muscle involvement (muscle glycogenoses): Types II, III, IV, V**
- **Liver involvement (liver glycogenoses): Types I, III, IV**
- **Types III and IV (late-onset type) may present with both muscle and liver involvement**
- **NO liver involvement >> V**

- autosomal recessive
- All types of glycogen storage diseases result in abnormal metabolism and product accumulation within cells.
- Type IV (Andersen's disease) is the only one **GSD** involved in Glycogen Synthesis. The rest are involved in Glycogen degradation.

**Diagnosis:** Periodic acid-Schiff stain is helpful in diagnosing glycogen storage disorders.

**Type I (Von Gierke's disease)**

- Relative frequency: ~25%
- Deficient enzyme
  - Type 1a
    - Glucose-6-phosphatase
      - Role of the enzyme >> Hydrolysis of glucose-6-phosphate to glucose and inorganic phosphate
  - Type 1b
    - Glucose-6-phosphate translocase
      - Role of the enzyme >> Transport of glucose-6-phosphate into the endoplasmic reticulum where it is hydrolyzed by glucose-6-phosphatase
- Characteristic features
  - Hepatomegaly
  - Severe fasting hypoglycemia, mild ketosis
  - Severe hyperlipidemia >> doll-like facies
  - Hyperuricemia
  - Lactic acidosis
  - Anemia
  - Failure to thrive

**Type II (Pompe's disease)**

- Relative frequency: ~15%
- Deficient enzyme: Lysosomal acid maltase deficiency
- Role of the enzyme: Glycogenolysis within the lysosome
- Characteristic features
  - Hypertrophic cardiomyopathy and/or conduction blocks
  - Proximal myopathy
  - Macroglossia
  - Failure to thrive

**Type III (Cori's disease)**

- Relative frequency: ~25%
- Deficient enzyme: debranching enzyme (alpha-1,6-glucosidase).

- Role of the enzyme: Glycogenolysis
- Characteristic features
  - Generalized muscle weakness and/or cramps
  - Hepatomegaly
  - Possibly cirrhosis (ascitis, splenomegaly)
  - Mild, fasting hypoglycemia and ketosis
  - Hyperlipidemia

**Type IV (Andersen's disease)**

- Relative frequency: ~3%
- Deficient enzyme: **Glycogen branching enzyme**
- Role of the enzyme: **Glycogenesis**
- Characteristic features
  - Proximal myopathy
  - Hepatomegaly
  - Possibly cirrhosis (ascites, splenomegaly)

**Type V (McArdle's disease)**

- Relative frequency: ~2%
- Deficient enzyme: Muscle phosphorylase (myophosphorylase)
- Role of the enzyme: Glycogenolysis
- Characteristic features
  - Generalized muscle weakness, exercise intolerance (with a second wind phenomenon) ,
  - Rhabdomyolysis and myoglobinuria

## McArdle's disease (Type V glycogen storage disease)

Often presents in adolescence with exercise intolerance, cramps and weakness

A history of painful muscle cramps that occur within a few minutes of initiating activity and which subside rapidly with rest, in conjunction with a raised serum CK, is highly suggestive of McArdle's disease

### Pathophysiology

**Autosomal recessive** mutation in myophosphorylase (PYGM) gene on chromosome 11 >> **myophosphorylase deficiency** (myophosphorylase is involved in the breakdown of glycogen to glucose) >> unable to release glucose from glycogen in muscle **(decreased muscle glycogenolysis).**

## Features

**Muscle pain and stiffness following exercise** (reversible)

- in the first few minutes of activity.
- Characterised by **'second wind' phenomenon**
  - after about 8 minutes most patients achieve a 'second wind' and can then continue exercise with less difficulty.
  - **Second wind** is a phenomenon in distance running, such as marathons (an athlete who is too tired to continue suddenly finds the strength to press on at top performance with less exertion).
  - **Mechanism >> metabolic switch**
    - When non-aerobic glycogen metabolism is insufficient to meet energy demands, physiologic mechanisms utilize alternative sources of energy such as fatty acids and proteins via aerobic respiration.
    - muscle fibers use fat as a source of energy.

## Investigations

- Creatine kinase levels are elevated in more than 90%
- NO increase in venous lactic acid levels following exercise testing.
- Urine study >> **Myoglobinuria** following exercise
- Muscle and/or liver biopsy >> jglycogen >> **PAS-positive granules** (initial tests)
- **DNA testing for the gene defects (Gene sequencing):** the **gold standard** for the diagnosis

## Management

- No specific treatment
- Dietary therapy (e.g., uncooked corn starch, glucose preparations) with the aim of preventing hypoglycemia and/or muscle symptoms
- Foods rich in **fructose** and **galactose should be avoided** in patients with GSD type I
- Advised to ingest snacks containing **sucrose** before exercise.
- Tourniquets should not be used during operative procedures

**The exertional thigh cramps, the presence of myoglobin and change in colour of urine after exercise suggests glycogen storage disease type V - McArdle's syndrome. the next most appropriate investigation >> Muscle biopsy which reveals subsarcolemmal deposits of glycogen appearing at the periphery of fibres.**

## Ehlers–Danlos syndrome (EDS)

The classic presentation of EDS involves hyperextensible skin, joint hypermobility, and a tendency to bleed easily.

- **Ehlers-Danlos syndrome** is a disorder of faulty collagen synthesis most commonly affecting collagen type III and V.
- Inheritance patterns and type of collagen affected vary (can be autosomal dominant or recessive)
- Collagen deficiencies in Ehlers-Danlos syndrome are often caused by problems with cross-linking.
- **Hypermobile Ehlers-Danlos syndrome** (EDS) is the **most common** of 13 subtypes.
  - Most hypermobile people are not aware of the fact and assume that everyone is as flexible as they are.
  - Most cases of hypermobile EDS, are inherited in an autosomal dominant manner.
  - associated with hypermobile joints, but skin features are much less prominent
  - Systemic features may include increased propensity to asthma, mild valve regurgitation and gastrointestinal (GI) symptoms, including constipation and hiatus hernia.
- The **most severe** form of Ehlers-Danlos syndrome is the **vascular type**.
  - deficiencies in type III collagen.
    - Type III collagen also known as reticulin, and is found primarily in granulation tissue, artery walls, skin, intestines and the uterus.
  - involves vascular and organ rupture due to type III collagen deficiency.
- The **classical type** of Ehlers-Danlos syndrome has deficiencies in **type V collagen**.
  - in which joint and skin manifestations predominate

  - associated with much more severe dermatological features, including hyperelastic skin that splits easily and marked propensity to bruising.
- **Kyphoscoliotic EDS is usually inherited in autosomal recessive fashion.**

## Features

| | |
|---|---|
| **Cardiovascular** | • Features of heart valve defects (particularly mitral valve prolapse)<br>• Features of aneurysms/dissections of the iliac, splenic, renal arteries, or the aorta<br>• Berry/saccular aneurysms of the cerebral arteries → features of subarachnoid hemorrhage |
| **Musculoskeletal** | • Joint hypermobility with tendency to dislocate<br>• Skeletal abnormalities (e.g., scoliosis)<br>• features of chronic pain syndrome and marfanoid habitus |
| **Skin** | • Tendency to bruise easily<br>• Skin hyperextensibility<br>• Frequent skin lacerations and poor skin healing (e.g., following surgery) |
| **Other** | • Hernias<br>• Features of organ rupture (e.g., shock, local pain), especially in vascular EDS |

## Diagnosis

- Definitive diagnosis for **all subtypes of EDS**, except hypermobile EDS, can be made by molecular genetic testing.
- The genetic basis of **hypermobile EDS** remains unknown and the diagnosis is made by clinical criteria only.
- A baseline echocardiogram with views of the aortic arch and aorta and regular reevaluations should be obtained to evaluate for **mitral valve** prolapse and any signs of aortic enlargement.

## Prognosis

- Life expectancy is typically normal with the exception of vascular EDS, which has a reduced life expectancy of ~ 50 year

# Mitochondrial inheritance disorders

## Kearns-Sayre syndrome

**Kearns-Sayre syndrome:**

- mitochondrial inheritance
- **onset < 20-years-old**
- Triad of:
  - **External ophthalmoplegia**
  - **Retinitis pigmentosa and**
  - **Heart block.**

### Overview

- mitochondrial DNA mutation.
- onset in patients < 20 years old

### Features

- external ophthalmoplegia >> Ptosis
- retinitis pigmentosa
- heart conduction defect
- sensorineural hearing loss is almost universal in those who survive into the fourth decade of life; this may not be fully corrected with hearing aids.
- Other associated features:
  - cerebellar ataxia,
  - raised cerebrospinal fluid (CSF) proteins,
  - proximal myopathy.
  - short stature
  - **multiple endocrinopathies** including diabetes mellitus, hypoparathyroidism, and Addison disease.

### Diagnosis

- Muscle biopsy may reveal ragged red fibers.
- Muscle histochemistry reveals **deficiency of cytochrome c oxidase** (mitochondrial respiratory chain enzyme).

### Prognosis

Patients rarely live beyond their 40s and there are no therapeutics currently available

# Molecular genetic investigation techniques

## Polymerase chain reaction (PCR)

PCR is a molecular genetic investigation technique.

The main advantage of PCR is its **sensitivity**: only **one** strand of sample DNA is needed to detect a particular DNA sequence.

It now has many uses including prenatal diagnosis, detection of mutated oncogenes and diagnosis of infections. PCR is also extensively used in forensics.

Prior to the procedure it is necessary to have two DNA oligonucleotide primers.

These are complimentary to specific DNA sequences at either end of the target DNA.

### Initial prep:

- Sample of DNA is added to test tube along with **two DNA primers**.
- A **thermostable DNA polymerase (Taq)** is added.

### The following cycle then takes place:

- Mixture is heated to almost boiling point causing denaturing (uncoiling) of DNA.
- Mixture is the allowed to cool: complimentary strands of DNA pair up, as there is an excess of the primer sequences they pair with DNA preferentially.

The above cycle is then repeated, with the amount of **DNA doubling each time.**

### Reverse transcriptase PCR:

- Used to **amplify RNA.**
- **RNA is converted to DNA by reverse transcriptase.**
- Gene expression in the form of **mRNA** (rather than the actually DNA sequence) can therefore be analysed.

**The main action of:**
**PCR** >>> **DNA** amplification.
**Reverse transcriptase PCR** >>> **RNA** amplification.

## Molecular biology techniques

The following table shows a very basic summary of molecular biology techniques:

| Technique | Description |
|---|---|
| **Southern blotting** | Detects **DNA.** |
| **Northern blotting** | Detects **RNA.** |
| **Western blotting** | Detects **proteins.**<br>Uses gel electrophoresis to separate native proteins by 3-D structure.<br>Examples include the **confirmatory** HIV test. |

**Molecular biology techniques:**

- SNOW (**S**outh - **NO**rth - **W**est): Detect:
- DROP (**D**NA - **R**NA - **P**rotein)

### Enzyme-linked immunosorbent assay (ELISA):

- A type of biochemical assay used to detect antigens and antibodies.
- A colour changing enzyme is attached to the antibody if looking for an antigen and to an antigen if looking for an antibody.
- The sample therefore changes colour if the antigen or antibody is detected.
- An example includes the **initial** HIV test.

The most suitable technique to **detect** and **quantify a viral protein** is >> **Western blotting (NOT** PCR).

A scientist is developing a new test for Bovine spongiform encephalopathy that uses gel electrophoresis to separate native **proteins** by 3-D structure. This is an

# Chromosomal diseases

## Chromosome abnormality

Chromosome anomalies usually occur when there is an error in cell division following meiosis or mitosis.

### Types

#### Numerical disorders

- called **aneuploidy** (an abnormal number of chromosomes), occurs when an individual either is:
  - missing a chromosome from a pair (monosomy)
    - e.g: Turner syndrome, (born with only one sex chromosome, an X).
  - has more than two chromosomes of a pair (trisomy, tetrasomy, etc.).
    - e.g: Down syndrome (trisomy 21)
- Unbalanced autosomal translocation
  - most likely to cause a severe phenotype
  - As a rule, the clinical effects of a chromosome abnormality reflect the amount of imbalance of genetic material. For example: all autosomal monosomies and most autosomal trisomies are incompatible with life, the exceptions being trisomy 13 (Patau syndrome), trisomy 18 (Edward syndrome) and trisomy 21 (Down syndrome); only the last of these carries a reasonable life expectancy.
- **Sex chromosome aneuploidy:**
  - This is associated with comparatively **less severe phenotypes,** e.g. Klinefelter syndrome (XXY) and Turner syndrome (XO).

#### Structural abnormalities: e.g:

- Duplications:
  - A portion of the chromosome is duplicated, resulting in extra genetic material.
  - e.g: Charcot-Marie-Tooth disease type 1A, caused by duplication of the gene encoding peripheral myelin protein 22 (PMP22) on chromosome 17.

## List of common Chromosomal disorders:

| Chromosome | disorders |
|---|---|
| **Chromosome 1** | variegate porphyria |
| **chromosome 3** | von Hippel Lindau (VHL) |
| **Chromosome 4** | Polycystic Kidney Disease (PKD2)<br>Huntington's disease<br>Achondroplasia |
| **Chromosome 6** | hereditary haemochromatosis |
| **Chromosome 7** | Cystic Fibrosis |
| **Chromosome 9** | Fredrich's ataxia |
| **Chromosome 11** | Sickle Cell Disease<br>Beta-Thalassemia |
| **Chromosome 12** | Phenylketonuria<br>**von Willebrand's disease** |
| **Chromosome 13** | Patau Syndrome.<br>Wilson Disease.<br>retinoblastoma |
| **Chromosome 15** | Marfan's Syndrome<br>Angelman Syndrome<br>Prader-Willi Syndrome<br>Tay-Sachs Disease. |
| **Chromosome 16** | Polycystic Kidney Disease (PKD1)<br>alpha- Thalassemia |
| **Chromosome 17** | Celiac Disease.<br>Charcot-Marie-Tooth Disease.<br>Neurofibromatosis (NF1) |
| **Chromosome 18** | Edward Syndrome |
| **Chromosome 19** | Myotonic Dystrophy |
| **Chromosome 21** | Down Syndrome |
| **Chromosome 22** | DiGeorge Syndrome.<br>Neurofibromatosis (NF2) |

# Down's syndrome: epidemiology and genetics

## Cytogenetics

| Mode | % of cases | Risk of recurrence |
|---|---|---|
| Nondisjunction | 94% | 1 in 100 if under mother < 35 years |
| Robertsonian translocation (usually onto 14) | 5% | 10-15% if mother is translocation carrier<br>2.5% if father is translocation carrier |
| Mosaicism* | 1% | |

The chance of a further child with Down's syndrome is approximately 1 in 100 if the mother is less than 35 years old.

If the trisomy 21 is a result of a translocation the risk is much higher.

**Nuchal scan** are offered on the NHS at around **11-13 weeks** and combined with other parameters, will give a risk of the unborn child having trisomy 21.

## Clinical features

- face: upslanting palpebral fissures, epicanthic folds, Brushfield spots in iris, protruding tongue, small low-set ears, round/flat face
- flat occiput
- single palmar crease, pronounced 'sandal gap' between big and first toe
- hypotonia
- congenital heart defects (40-50%, see below)
- duodenal atresia
- Hirschsprung's disease

### Cardiac complications

- multiple cardiac problems may be present
- endocardial cushion defect (most common, 40%, also known as atrioventricular septal canal defects)
- **ventricular septal defect (c. 30%)**
- **secundum atrial septal defect (c. 10%)**
- **tetralogy of Fallot (c. 5%)**
- **isolated patent ductus arteriosus (c. 5%)**

### Later complications

- **subfertility**: males are almost always infertile due to impaired spermatogenesis. Females are usually subfertile, and have an increased incidence of problems with pregnancy and labour
- learning difficulties
- **short stature**
- **repeated respiratory infections** (+hearing impairment from glue ear)
- **acute lymphoblastic leukaemia**
- **hypothyroidism**
- **Alzheimer's disease**
- **atlantoaxial instability**

## Turner's syndrome

Turner's syndrome is a chromosomal disorder affecting around **1 in 2,500** females.

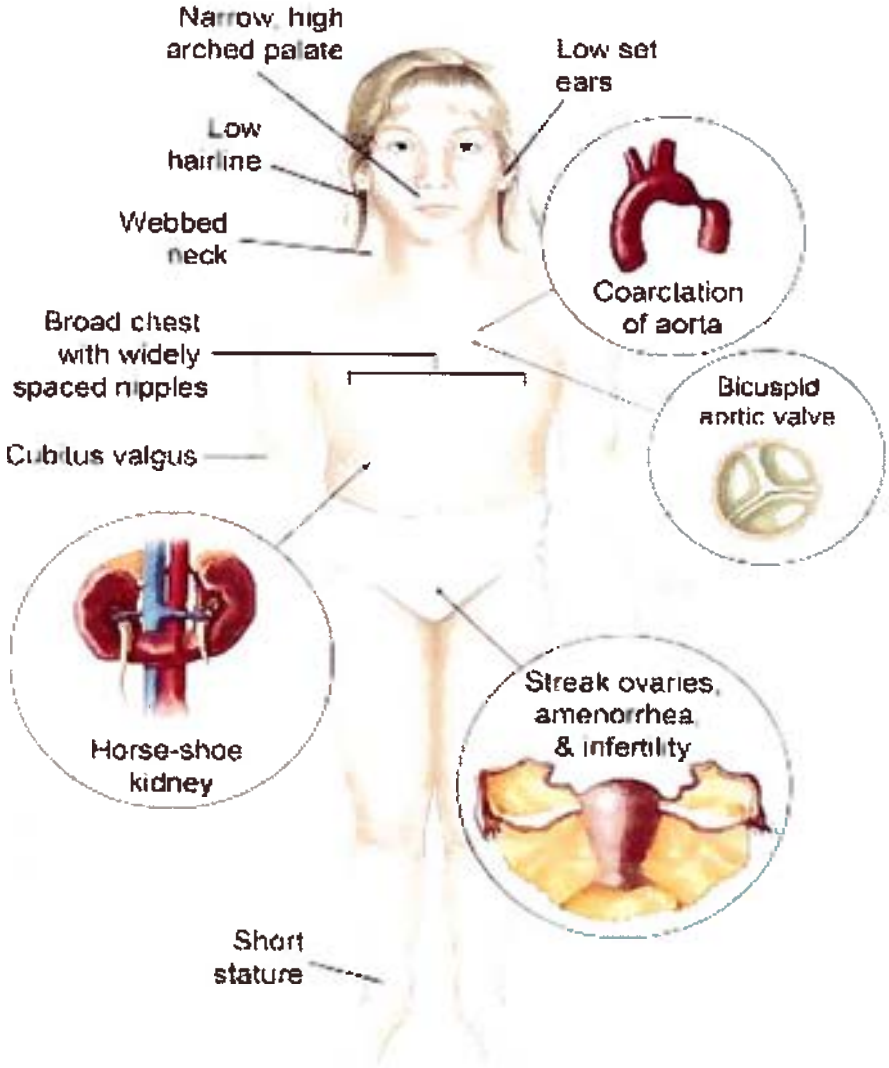
It is caused by either the presence of **only one sex chromosome (X)** or a deletion of the short arm of one of the X chromosomes.

Turner's syndrome is **denoted as 45, XO or 45, X.**

### Features:

- **Short stature.**
- Shield chest, widely spaced nipples.
- **Webbed neck.**
- **Bicuspid aortic valve (15%), Coarctation of the aorta** (5-10%)
- **Primary amenorrhoea.**
- Cystic hygroma (often diagnosed prenatally).
- **High-arched palate.**
- Short fourth metacarpal.
- Multiple pigmented naevi.
- Lymphoedema in neonates (especially feet).
- There is also an increased incidence of autoimmune disease Yo (especially **autoimmune thyroiditis**) and **Crohn's disease**.
- **horseshoe kidney**: the most common renal abnormality in Turner's syndrome.
- gonadotrophin levels will be elevatedome

## Turner syndrome




**Turner's syndrome** > the most common cardiac defect is bicuspid aortic valve **EX**: female with 1ry amenorrhea + HTN >>>>> think of: Turner syndrome or congenital adrenal hyperplasia.

# Klinefelter's syndrome

- It is a sex chromosome disorder affecting **1:1000** male births.
- Typically associated with **karyotype 47, XXY** or XXXYY or XXYY
- It involves the loss of Leydig cells and seminiferous tubular dysgenesis.
- The rate of chromosomal non dysjunction increases with increasing the **maternal** and **paternal ages, each** parent contributing **50%** of the risk.
- Around 60% of Klinsfelter's does not survive the fetal period.

## Features:

- Often **taller** than average
- **Lack of secondary sexual characteristics**
- **Small, firm testes**
- **Infertile**
- **Gynaecomastia** - increased incidence of **breast cancer**
- **Elevated gonadotrophin** levels (↑ **FSH and LH**)
- With **low testosterone**.
- Bone mineral density is decreased, and they are at increased risk of **osteoporotic** fractures.
- LDL levels may be normal or increased, **low HDL** and **high triglyceride** levels with increased cardiovascular risk and this at least in part may stem from **abnormalities in lipid metabolism**.

**Diagnosis** is by **chromosomal analysis** **(Karyotyping).**

## Treatment:

- Androgen replacement
- Cosmetic correction of gynecomastia
- Psychosocial counselling.

**EX: Male** pt. with **Colles** fracture after **minor** trauma, **DEXA** T-score **-3**, **depression**, **impotence**, loss of libido, sparse secondary sexual hair, small testis >>>? **Klinefelter's** >>> ttt: **Testosterone** which will improve bone mineralization, good impact on his sexual life and depressive symptoms.

Unfortunately, due to late diagnosis of Klinefelter's, a significant number of patients begin testosterone replacement therapy far too late

## Angelman syndrome

### Overview

- Angelman syndrome is a genetic condition characterized by a mutation on the **maternal copy** of **chromosome 15**.
- occurs as a result of a phenomena known as genomic **imprinting**.
- The imprinted copy of the gene is silenced through methylation or histone modification.
- Normally, certain paternal alleles on chromosome 15 are silenced and only the maternal alleles are expressed. However, in Angelman syndrome, the maternal alleles are mutated. Hence, the patient will have disease since only the mutated maternal alleles are active.

### Features

- developmental delay,
- Intellectual disability
- **Seizures, Ataxia**
- **Unprovoked laughter**
- Large mouth with tongue protrusion.
- Hypo-pigmentation with blond hair

**Diagnosis:** genetic studies showing loss of function of the **UBE3A** gene.

## McCune-Albright syndrome

McCune-Albright syndrome is not inherited, it is due to a random, somatic mutation in the GNAS gene.

### Features

- precocious puberty
- **cafe-au-lait spots**
- **polyostotic fibrous dysplasia**
- short stature

## Genetic anticipation

**Anticipation: successive generations present with symptoms at an earlier age**

### Definition

The 'classic' definition of anticipation is **earlier onset** in successive generations. However, in most cases, an increase in the severity of symptoms is also noted.
If both options (earlier onset and sever symptoms) are presented, then the earlier onset should be chosen

### Example

A man **aged 33** presents with features of Huntington's disease (depression, weight loss and choreiform movements).
He informs you that his father had similar symptoms **aged 50**, his grandfather **aged 75** and both deteriorated in terms of mobility and mental state, and eventually died.

### Occur in

- Huntington's disease,
- myotonic dystrophy
- fragile X syndrome.

## Fragile X syndrome (large ear, large testes)

In addition to moderate to severe **mental retardation**, other characteristics of individuals with Fragile X syndrome may include:

- The face is typically **long and narrow**, with a **high arched palate** and **large ears.**
- **Macroorchidism (large testes).**
- Prognathism
- **Speech delays**
- Prominent forehead
- Double-jointedness
- Autistic symptoms, and
- Occasional self-mutilation.
- Otitis media, strabismus, and dental problems may be present.

### Other common characteristics include:

- Hyper-extensible joints
- Hypotonia, and
- Heart problems, including mitral valve prolapse.

In post pubertal males, **abnormally large testes are a distinctive feature.**

### The following can occur in young children:

- **Delayed motor development**
- Hyperactivity
- Behavioural problems
- Toe walking, and
- Occasional seizures.

# Antibodies and immunological markers

## Erythrocyte sedimentation rate (ESR)

### Causes of a high ESR:

- Temporal arteritis
- Myeloma
- Other connective tissue disorders e.g. SLE
- Other malignancies
- Infection
- Other factors which raise ESR: increasing **age**, **female** sex, **anaemia**.

**Causes of a Low ESR:** **Polycythaemia.**
**Afibrinogenemia/hypofibrinogenemia**

## Acute phase reactant proteins

### Acute phase proteins:

- **CRP**
- **Ferritin**
- **Fibrinogen**
- **Haptoglobin**
- **Complement**
- **Pro-calcitonin**
- **Alpha-1 antitrypsin**
- **Ceruloplasmin**
- **Serum amyloid A**
- negative acute phase proteins **Serum amyloid P** component (It has a more role in mice)

During the acute phase response the **liver decreases the production** of other proteins (sometimes referred to as**).** Examples include:

- **Albumin**
- **Transthyretin** (formerly known as **prealbumin**)
- **Transferrin**
- **Retinol binding protein**
- **Cortisol binding protein**

**NB: ESR** is **not** considered as an **acute phase proteins.**

# ANCA

## cANCA = Wegener's; pANCA = Churg-Strauss + others

**There are two main types of anti-neutrophil cytoplasmic antibodies (ANCA):**

- cytoplasmic (cANCA) and
- perinuclear (pANCA)

**For the exam, remember:**

- cANCA - Wegener's granulomatosis
- pANCA - Churg-Strauss syndrome + others (see below)

## cANCA

- most common **target serine proteinase 3 (PR3)**
- some correlation between cANCA levels and disease activity
- Wegener's granulomatosis, positive in > 90%
  - In Wegener's, the level of PR3 antibody and ANCA titre are **related to disease activity** and the antibodies typically disappear when the disease is in remission.
- microscopic polyangiitis, positive in 40%

## pANCA

- most common **target is myeloperoxidase (MPO)**
- cannot use level of pANCA to monitor disease activity
- associated with immune crescentic glomerulonephritis (positive in c. 80% of patients)
- microscopic polyangiitis, positive in 50-75%
- Churg-Strauss syndrome, positive in 60%
- primary sclerosing cholangitis, positive in 60-80%
- Wegener's granulomatosis, positive in 25%
- **Other causes of positive ANCA (usually pANCA)**
  - inflammatory bowel disease (UC > Crohn's)
  - connective tissue disorders: RA, SLE, Sjogren's
  - autoimmune hepatitis

**Exam: Which one of the following statements is true regarding cytoplasmic anti-neutrophil cytoplasmic antibodies (cANCA)?**
**>> Associated with Wegener's granulomatosis**

| Antibody | Associated condition |
|---|---|
| **Antinuclear antibodies (ANA)** | • Younger women often have low **(ANAs)**<br>• **increase with age**<br>• ANA positivity with antiphospholipid antibody syndrome (APL) suggests secondary APL, ie in association with a connective tissue disease.<br>• The common tests used for detecting and screening ANAs are indirect immunofluorescence and enzyme-linked immunosorbent assay (ELISA).<br>• Although positive titres of 1:160 or higher are strongly associated with autoimmune disorders, they are also found in 5% of healthy individuals<br>• Positive titres of less than 1:160 are present in up to 20% of the healthy population, especially the elderly. |
| **Anti-Ro (SS-A)** and **anti-La** (SS-B) | **Anti-Ro**<br>Sjögren's syndrome (50–70%)<br>SLE with cutaneous involvement (30%)<br>anti-Ro can cross the placenta and cause neonatal lupus in babies. |
| **Anti-Smith (Anti-Sm)** | **very specific marker for SLE** (99%)<br>sensitivity (20%)<br>**not associated with disease activity.** |
| **Anti-nuclear ribonucleoprotein (anti-nRNP)** also known as anti-U1 RNP | highly associated with **mixed connective tissue disease.**<br>SLE (30 – 40%) |
| **Anti-double stranded DNA (anti-dsDNA)** | **very specific marker for SLE, (nearly 100%).**<br>sensitivity (85%).<br>**Correlate with disease activity in SLE**.<br>also linked with lupus nephritis. |
| **Anti-histone** | **drug induced lupus (75–95%)**<br>idiopathic SLE (75%)<br>Unlike anti-dsDNA, these antibodies do not fix complement. |
| **anti-glycoprotein-210 (anti-gp210) and anti-nucleoporin 62 (anti-p62)** | primary biliary cirrhosis (PBC) (25–30%). |

| | |
|---|---|
| **Anti-centromere** | **limited cutaneous systemic sclerosis**, also known as CREST syndrome,<br>primary biliary cirrhosis |
| **Thyroid autoantibodies (microsomal and thyroglobulin)** | **Hashimoto's thyroiditis (70-90% microsomal: 75-95% thyroglobulin)**<br>Pernicious anaemia (55% microsomal) |
| **Anti-Scl-70** | **diffuse cutaneous scleroderma (40%),**<br>limited cutaneous involvement (10%).<br>SLE (5%)<br>The antigenic target of anti-Scl-70 antibodies is topoisomerase I |
| **Antireticulin** | Coeliac disease (37%)<br>Crohn's disease (24%) |
| **Gastric parietal cell antibody** | **Pernicious anaemia (>90%)**<br>Atrophic gastritis (60%)<br>Autoimmune thyroid disease (33%) |
| **Anti-mitochondrial antibody** | **Primary biliary cirrhosis (60-94%)** |
| **Anti-smooth muscle antibody** | **Chronic active hepatitis** (40-90%)<br>Primary biliary cirrhosis (30-70%)<br>Idiopathic cirrhosis (25-30%)<br>Viral infections (80%) |
| **Anti-sp100** | primary biliary cirrhosis (PBC) (20–30%).<br>**very specific marker of the disease.** |
| Anti-PM-Scl | polymyositis/systemic sclerosis (PM/SSc) overlap syndrome (50%). |
| Anti-Hu | small-cell lung cancer, neuroblastoma and prostatic cancer |
| Intrinsic factor antibodies | pernicious anaemia, and hence (subacute combined degeneration of the spinal cord) secondary to vitamin B12 deficiency |
| **Anti-Ri** | neuroblastoma (children) and fallopian or breast cancer (adults), resulting in paraneoplastic opsoclonus myoclonus ataxia (POMA). |
| **Anti-Yo** | gynaecological tumours and breast cancer, |
| **Anti-Tr** | Hodgkin's disease, resulting in cerebellar degeneration. |
| **Anti-Ta (Ma2)** | testicular tumours, and can lead to limbic or brain stem encephalomyelitis. |
| **Anti-endomysial / gliadin / transglutaminase** | coeliac disease, and related vitamin B-1 deficiency may lead to Wernicke's encephalopathy and Korsakoff's psychosis |

| | |
|---|---|
| Tissue transglutaminase antibody ('tTGA') & Endomysial antibody ('EMA') | The most accurate blood tests for coeliac disease |
| *double-stranded* DNA (ds-DNA) **Anti-dsDNA** | highly specific for SLE. |
| Antibodies that bind single-stranded denatured DNA (ss-DNA) | present in 90% of patients with SLE, but also in drug-induced lupus and other connective tissue disorders. |
| **Anti-Jo** | **Polymyositis** |
| **Rheumatoid factor** | **Rheumatoid arthritis, Sjogren's (90%), SLE (30%)** ***5% of normal population*** |

**The only two auto-antibodies which have a role in monitoring disease activity**
(there is correlation between levels and disease activity)

1. Anti-ds DNA antibodies in systemic lupus erythematosus (SLE)
2. Circulating anti-neutrophil cytoplasmic antibody (cANCA) in Wegener's granulomatosis.

The ESR is a non-specific marker of inflammation and depends on both the size, shape and number of **RBCs** and the concentration of **plasma proteins** such as fibrinogen, alpha2-globulins and gamma globulins.

## Nitric oxide (NO)

Previously known as endothelium derived relaxation factor, nitric oxide (NO) has emerged as a molecule which is integral to many physiological and pathological processes.

It is **formed from L-arginine** and oxygen by nitric oxide synthetase (NOS).

An inducible form of NOS has been shown to be present in **macrophages**.

Nitric oxide has a **very short half-life (seconds)**, being **inactivated by oxygen free radicals**.

### Effects:

- Acts on **Guanylate cyclase receptor** leading to raised **intracellular cGMP** levels and therefore **decreasing Ca2+ levels.**
- **Vasodilation**, mainly **venodilation.**
- **Inhibits platelet aggregation.**

Nitric oxide > ↑cGMP>>↓Ca++ >>>> vasodilation + inhibits platelet aggregation

### Clinical relevance:

- **Underproduction** of NO is implicated in **hypertrophic pyloric stenosis**.
- **Lack** of NO is thought to promote **atherosclerosis**.
- In sepsis **increased** levels of NO contribute to **septic shock**.
- Organic nitrates (metabolism produces NO) is widely used to treat cardiovascular disease (e.g. angina, heart failure).
- Sildenafil is thought to potentiate the action of NO on penile smooth muscle and is used in the treatment of erectile dysfunctions.

## Endothelin

Endothelin is a potent, long-acting **vasoconstrictor** and **bronchoconstrictor**.

It is secreted initially as a prohormone by the **vascular endothelium** and later converted to ET-1 by the action of endothelin converting enzyme.

It acts via interaction with a G-protein linked to phospholipase C leading to calcium release.

Endothelin is thought to be important in the pathogenesis of many diseases including primary pulmonary hypertension (endothelin antagonists are now used), cardiac failure, hepatorenal syndrome and Raynaud's.

### Promotes release:

- **Angiotensin II**
- **ADH**
- **Hypoxia**
- **Mechanical shearing forces**

### Inhibits release:

- **Nitric oxide**
- **Prostacyclin**

### Raised levels in:

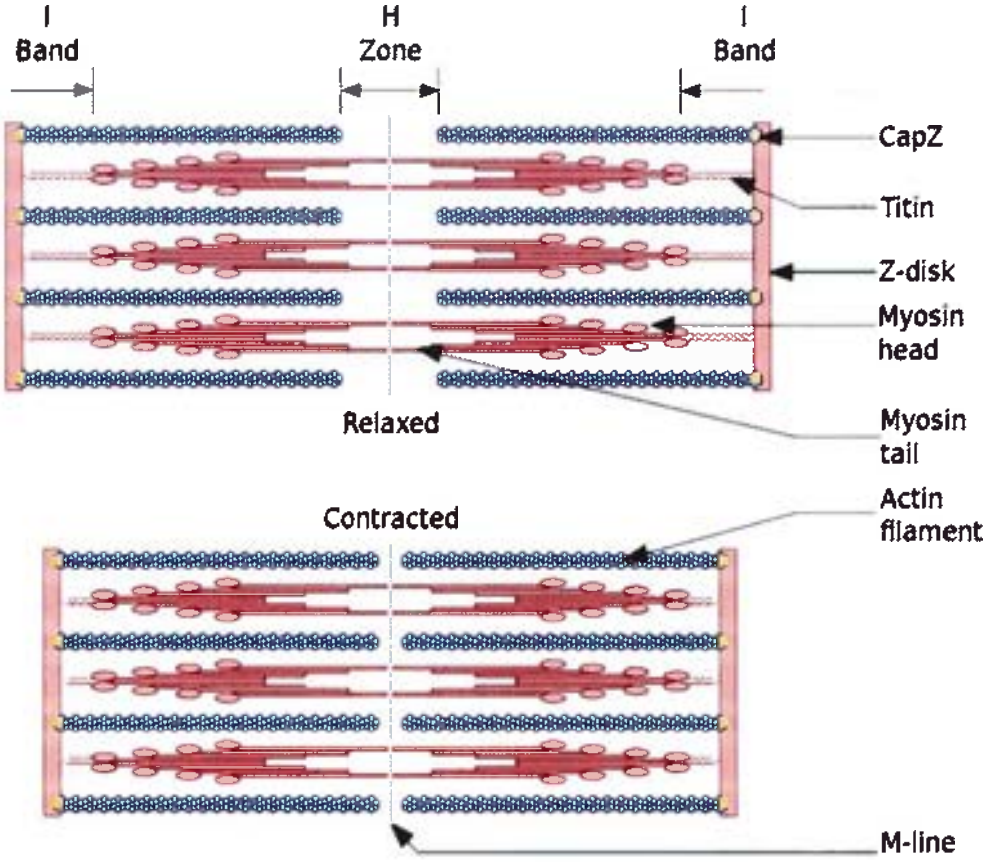
- MI
- Heart failure
- ARF
- Asthma
- Primary pulmonary hypertension

# Important anatomical considerations

## Muscle contraction

**Major steps:**

- action potential reaches the neuromuscular junction, causing a calcium ion influx through voltage-gated calcium channels
- the calcium influx causes the release of acetylcholine into the extracellular space
- the acetylcholine activates nicotinic acetylcholine receptors causing an influx of sodium, triggering an action potential
- the action potential spreads through the T-tubules
- the depolarization activates L-type voltage-dependent calcium channels (dihydropyridine receptors) in the T-tubule membrane, which are close to calcium-release channels (ryanodine receptors) in the adjacent sarcoplasmic reticulum
- this causes the sarcoplasmic reticulum to release calcium
- calcium binds to troponin C (found on actin-containing thin filaments) causing a conformational change, allowing tropomyosin to move, unblocking the binding sites
- myosin binds to the newly released binding site releasing ADP, pulling the Z bands towards each other
- ATP binds to myosin, releasing actin


I Band
H Zone
I Band
CapZ
Titin
Z-disk
Myosin head
Myosin tail
Actin filament
Relaxed
Contracted
M-line

| Component | Notes |
|---|---|
| Sarcomere | Basic unit of muscles that gives skeletal and cardiac muscles their striated appearance. Segment between two adjacent Z-lines |
| I-band | Zone of thin filaments that is not superimposed by thick filaments |
| A-band | Contains the entire length of a single thick filament |
| H-zone | Zone of the thick filaments that is not superimposed by the thin filaments |
| M-line | Middle of the sarcomere, cross-linking myosin |
| Sarcoplasmic reticulum | Releases calcium ion in response to depolarization |
| Actin | Thin filaments that transmit the forces generated by myosin to the ends of the muscle |
| Myosin | Thick filaments<br>Binds to thin filament |
| Titin | Connects the Z-line to the thick filament, altering the structure of tropomyosin |
| Tropomyosin | Covers the myosin-binding sites on actin |
| Troponin-C | Binds with calcium ions |
| T-tubule | Is an invagination of the sarcoplasmic reticulum<br>Helps co-ordinate muscular contraction |

The table below shows the types of skeletal muscle fibres (type II fibres are simplified into one category):

| | Type I | Type II |
|---|---|---|
| **Contraction time** | Slow | Fast |
| **Colour** | Red (due to presence of myoglobin) | White (due to absence of myoglobin) |
| **Main use** | Sustained force | Sudden movement |
| **Major fuel** | Triglycerides | ATP |
| **Mitochondrial density** | High | Low |

**Mnemonic for type I fibres - 'One Slow, Fat, Red Ox'**

# Upper limb anatomy

The information below contains selected facts which commonly appear in examinations:

| Nerve | Motor | Sensory | Typical mechanism of injury & notes |
|---|---|---|---|
| Musculocutaneous nerve (C5-C7) | Elbow flexion (supplies biceps brachii) and supination | Lateral part of the forearm | Isolated injury rare - usually injured as part of brachial plexus injury |
| **Axillary nerve** (C5, C6) | **Shoulder abduction** (deltoid muscle) | Inferior region of the deltoid muscle | Humeral neck fracture/dislocation Results in flattened deltoid |
| Radial nerve (C5-C8) | Extension (forearm, wrist, fingers, thumb) | Small area between the dorsal aspect of the 1st and 2nd metacarpals | Humeral midshaft fracture<br><br>Palsy results in wrist drop |
| Median nerve (C6, C8, T1) | LOAF* muscles **Features** depend on the site of the lesion:<br>• wrist: paralysis of thenar muscles, opponens pollicis<br>• elbow: loss of pronation of forearm and weak wrist flexion | Palmar aspect of lateral 3½ fingers | Wrist lesion → carpal tunnel syndrome |
| **Ulnar** nerve (C8, T1) | Intrinsic hand muscles **except LOAF*** Wrist flexion | Medial 1½ fingers | Medial epicondyle fracture Damage may result in a **'claw hand'** |
| Long thoracic nerve (C5-C7) | **Serratus anterior** | | Often during sport e.g. following a blow to the ribs. Also possible complication of mastectomy **Damage results in a winged scapula** |

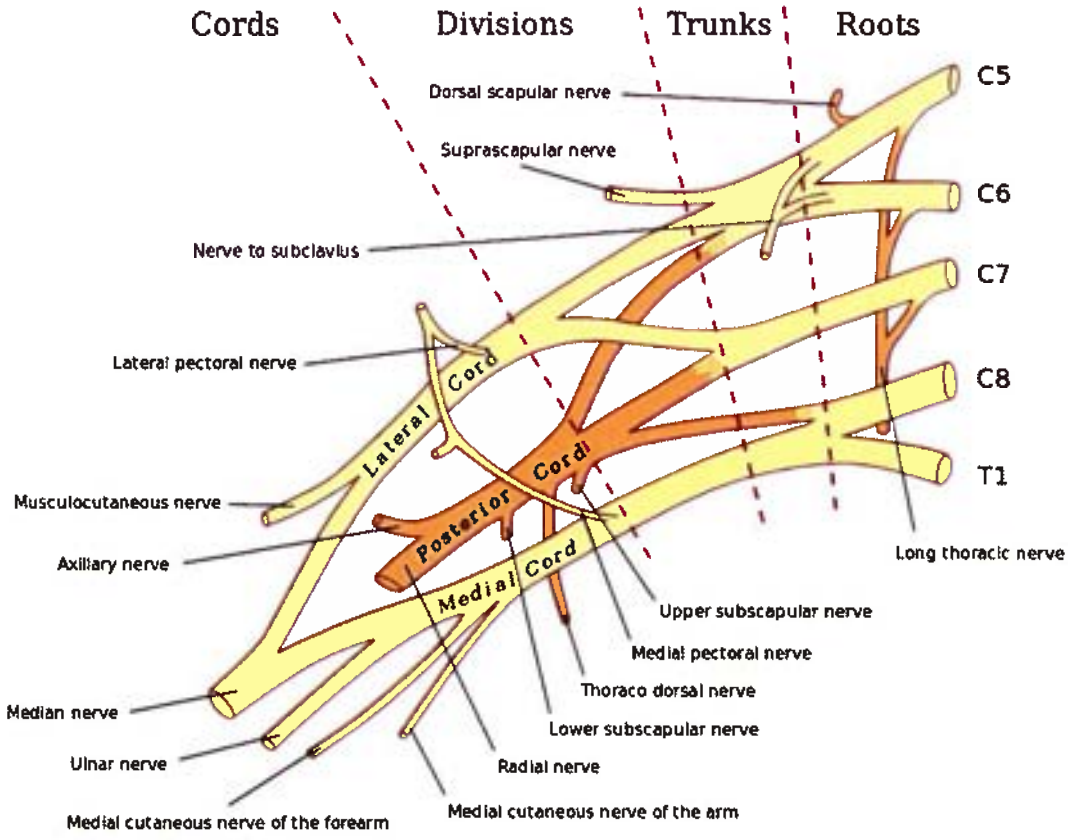



Diagram of the brachial plexus

## Erb-Duchenne palsy ('waiter's tip'):

- Due to damage of the **upper trunk of the brachial plexus (C5, C6).**
- May be secondary to **shoulder dystocia** during birth.
- The arm hangs by the side and is internally rotated, elbow extended.

## Klumpke injury:

- Due to damage of the **lower trunk of the brachial plexus (C8, T1**).
- As above, may be secondary to shoulder dystocia during birth. Also may be caused by a sudden upward jerk of the hand.
- Associated with **Horner's syndrome.**

## *LOAF muscles:

- **Lateral 2 lumbricals**
- **Opponens pollis**
- **Abductor pollis brevis**
- **Flexor pollis brevis**

# Lower limb anatomy

The information below contains selected facts which commonly appear in examinations:

| Nerve | Motor | Sensory | Typical mechanism of injury & notes |
|---|---|---|---|
| **Femoral nerve** | Knee extension, thigh flexion | Anterior and medial aspect of the thigh and lower leg | Hip and pelvic fractures<br>Stab/gunshot wounds |
| **Obturator nerve** | Thigh adduction | Medial thigh | Anterior hip dislocation |
| Lateral cutaneous nerve of the thigh | None | Lateral and posterior surfaces of the thigh | Compression of the nerve near the ASIS → meralgia paraesthetica, a condition characterised by pain, tingling and numbness in the distribution of the lateral cutaneous nerve |
| **Tibial nerve** | Foot plantarflexion and inversion | Sole of foot | Not commonly injured as deep and well protected.<br>Popliteral lacerations, posterior knee dislocation |
| Common peroneal nerve | Foot dorsiflexion and eversion<br>Extensor hallucis longus | Dorsum of the foot and the lower lateral part of the leg | Injury often occurs at the neck of the fibula<br>Tightly applied lower limb plaster cast<br>Injury causes foot drop |
| **Superior gluteal nerve** | Hip abduction | None | Misplaced intramuscular injection<br>Hip surgery<br>Pelvic fracture<br>Posterior hip dislocation<br>**Injury results in a positive Trendelenburg sign** |
| **Inferior gluteal nerve** | Hip extension and lateral rotation | None | Generally injured in association with the sciatic nerve<br>Injury results in difficulty rising from seated position.<br>Can't jump, can't climb stairs |

# Radial nerve

**Overview:** Arises from the posterior cord of the brachial plexus (**C5-8**).
**Motor to:** **Extensor** muscles (forearm, wrist, fingers, thumb).
**Sensory to:**

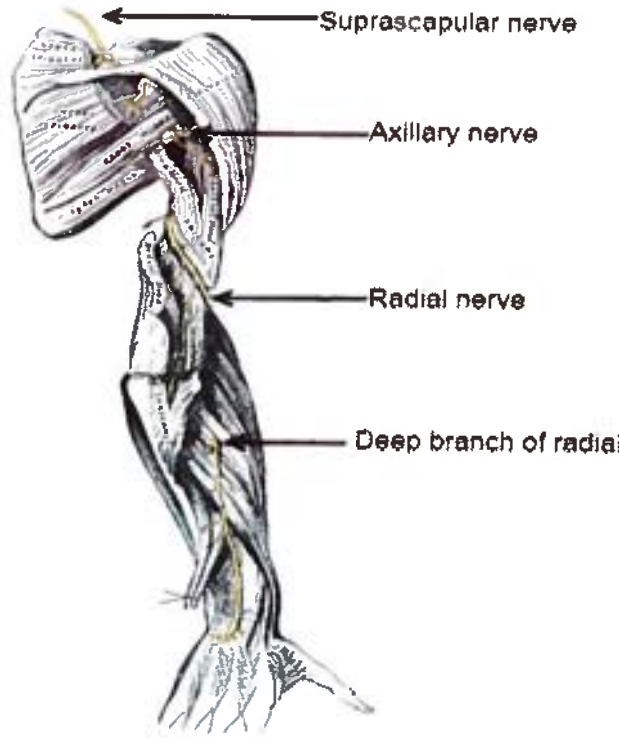
- **Dorsal** aspect of **lateral 3 1/2 fingers.**
- However, only small area between the dorsal aspect of the 1st and 2nd metacarpals is unique to the radial nerve.

**Patterns of damage:**

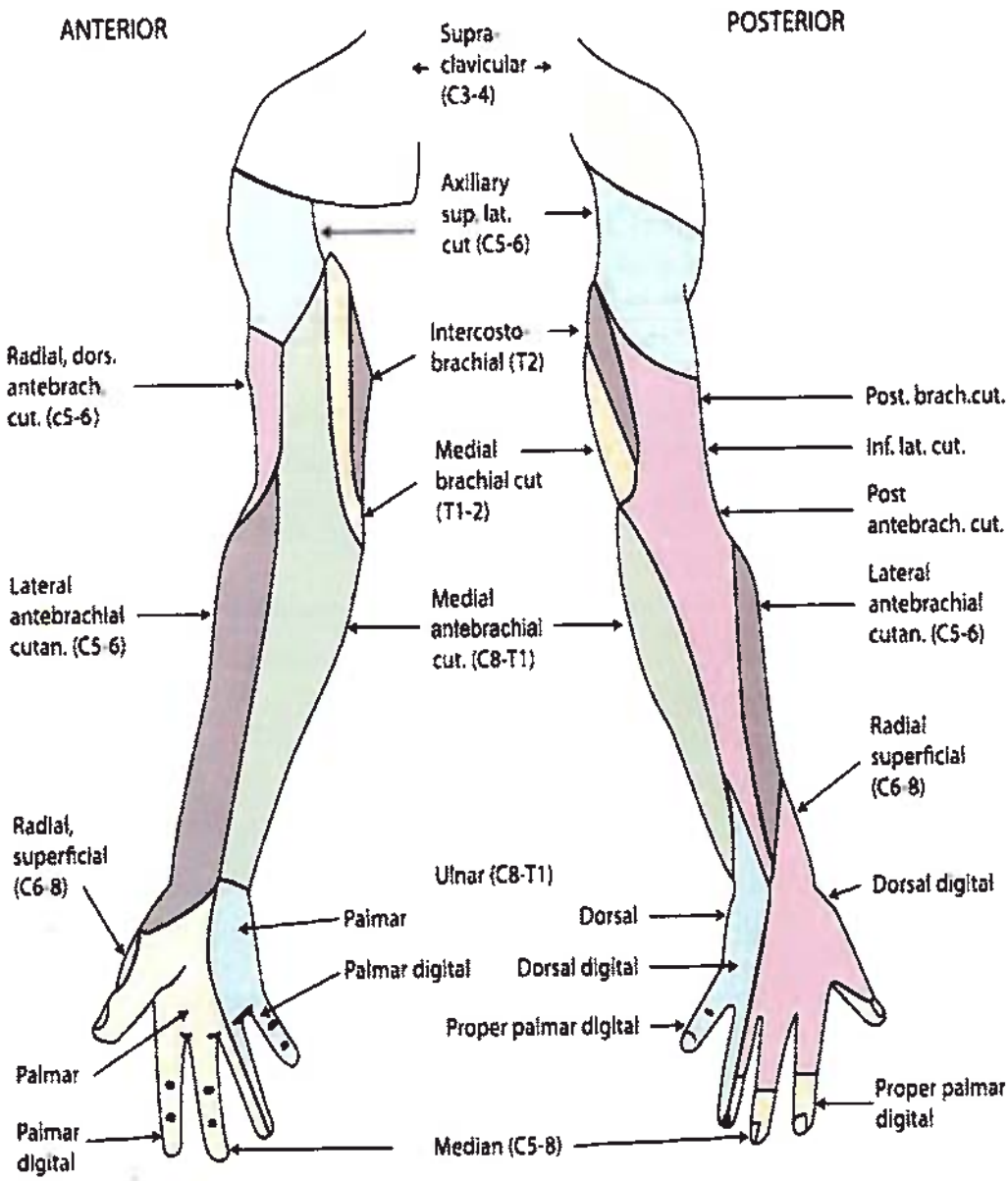
- **Wrist drop.**
- Sensory loss to small area between the dorsal aspect of the 1st and 2nd metacarpals.

**Axillary damage:**

- **As above.**
- **Paralysis of triceps.**




In the image above the relationships of the radial nerve can be appreciated




The cutaneous sensation of the upper limb- illustrating the contribution of the radial nerve

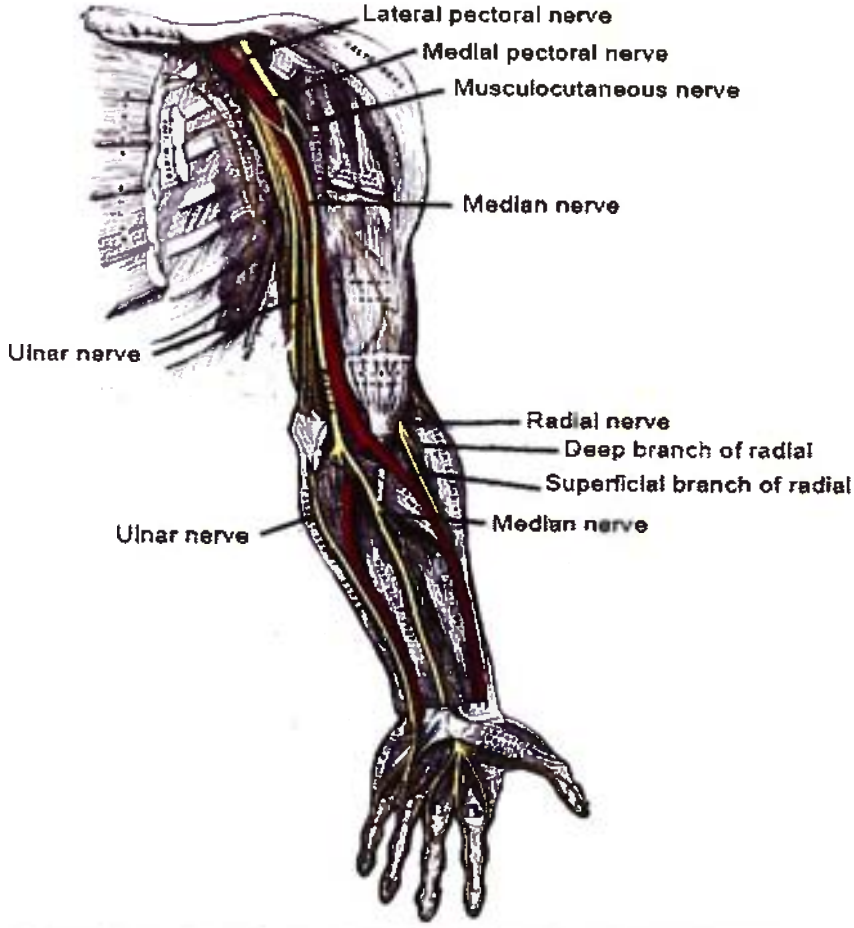
# Ulnar nerve

**Overview:** Arises from medial cord of brachial plexus (C8, T1)

**Motor to:**

- **Ulnar >>> All** Intrinsic **hand** muscles **except LOAF***
- Medial two lumbricals
- Adductor pollicis
- **Interossei**
- Hypothenar muscles: abductor digiti minimi, flexor digiti minimi
- Flexor carpi ulnaris

**Sensory to:** **Medial** 1 1/2 fingers (**palmar** and **dorsal** aspects)



## Patterns of damage

### Damage at wrist:

- **'Claw hand'** - hyperextension of the metacarpophalangeal joints and flexion at the distal and proximal interphalangeal joints of the 4th and 5th digits
- Wasting and paralysis of **intrinsic hand muscles** (**except** lateral two lumbricals)
- Wasting and paralysis of **hypothenar** muscles
- Sensory loss to the medial 1 1/2 fingers (palmar and dorsal aspects)

### Damage at elbow:

- As above (however, **ulnar paradox - clawing** is **more severe** in **distal** lesions).
- Radial deviation of wrist.

# Common peroneal nerve lesion

The **sciatic nerve** divides into the **tibial** and **common peroneal nerves**.
Injury often occurs at the **neck of the fibula**.
The **most characteristic feature** of a common peroneal nerve lesion is **foot drop.**

## Other features include:

- **Weakness** of **foot dorsiflexion.**
- **Weakness** of **foot eversion.**
- **Weakness** of **extensor hallucis longus.**
- **Sensory loss** over the **dorsum of the foot** and **the lower lateral part of the leg.**
- **Wasting** of the **anterior tibial** and **peroneal muscles.**

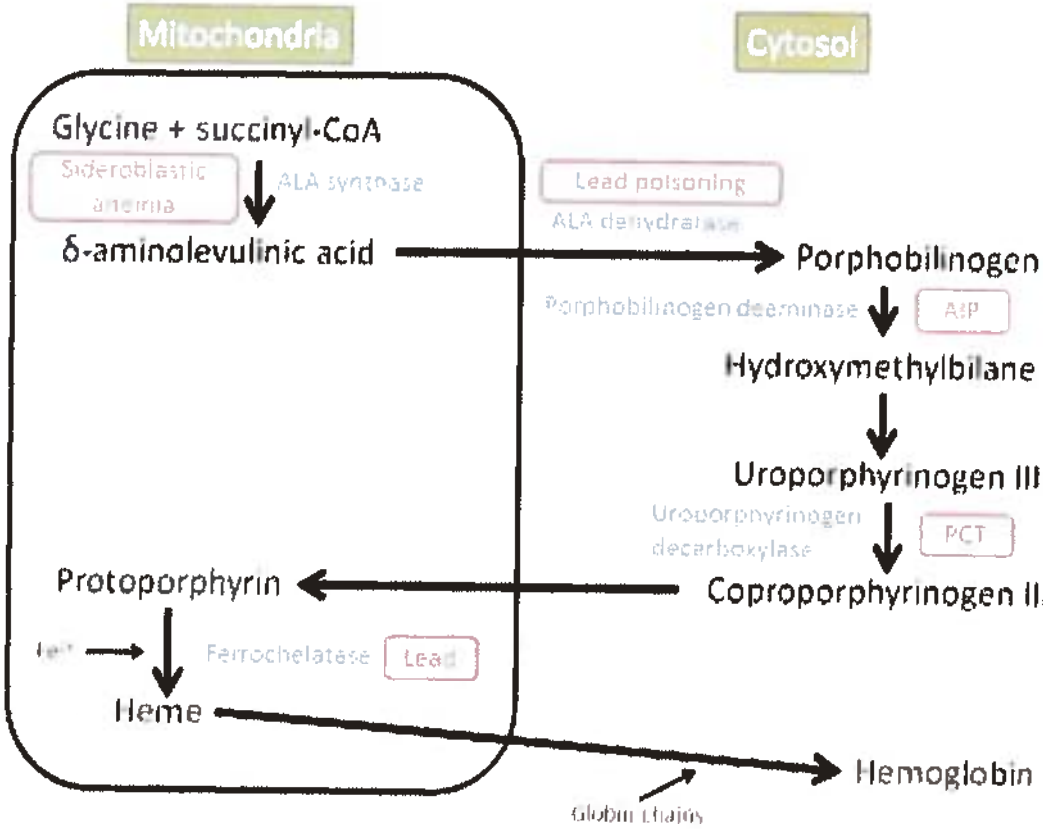
The degree of wasting will depend on **how long** the palsy had been present.

# Miscellaneous

## Porphyrias

**Overview:**

- Abnormality in enzymes responsible for the **biosynthesis of haem.**
- Results in **overproduction** and **excretion** of intermediate compounds called **porphyrins**.
- May be acute or non-acute.




AIP>>porphobilinogen deAminase; PCT >> uroporphyrinogen deCarboxylase

## Acute intermittent porphyria (AIP):

- It is a **rare Autosomal dominant.**
- **Defect** in RBCs **porphobilinogen (PBG) deaminase,** which is an enzyme involved in the biosynthesis of haem, so increased urinary excretion of the haem precursor **porphobilinogen (PBG) in urine.**
- All attacks of porphyria **increase activity** of **hepatic 5-aminolevulinate (ALA) synthase.**
- **AIP is** caused by **toxic accumulation of porphobilinogen (PBG) and delta aminolaevulinic acid (DALA).**
- The relation between these biochemical abnormalities and the neuronal dysfunction which underlies all the features of an acute attack is uncertain.
- **Female** (5:1) and **20-40 year olds** more likely to be affected.
- Only rarely presents before puberty with **90%** of affected individuals remain **asymptomatic throughout their lives.**
- Typically present with **abdominal** and **neuropsychiatric** symptoms (**Neuro-visceral crisis**).
- **Acute abdominal pain and vomiting** are the **commonest** presenting features **(90%)**, often associated with **neuropsychiatric** symptoms, ranging from anxiety and depression to fits and frank psychosis.
- Symptoms include **severe neuropathic abdominal pain with peritonism** (85-95%), **vomiting** (50-90%), **paresis** (40-70%) and **seizures** (10-20%).
- Patients feel **normal between attacks.**
- **Hypertension** and **tachycardia** common.
- AIP is also associated with a **mild increase in temperature** and **hyponatraemia (SIADH).**
- **Urine** turns **deep red on standing.**
- Photosensitivity is unusual in AIP and patients excrete urinary PBG between and during acute attacks.
- **Raised urinary porphobilinogen (PBG)** greater than **4 times the upper limit** of normal (elevated between attacks and to a greater extent during acute attacks).
- **Raised serum** levels of **delta aminolaevulinic acid** (**DALA**) and **porphobilinogen.**
- Faecal porphyrin excretion is usually normal or slightly increased.
- **Two** procedures have been shown to **decrease** the activity of ALA synthase: **carbohydrate loading** and **parenteral infusion of Haem.**

- **Management includes:**
  - Analgesia - **opiates** (morphine) are often required.
  - **High carbohydrate intake (IV Glucose)**
  - And in severe attacks (**Haematin**) **haem arginate IV infusion: is the ttt of choice** which inhibit haem production and thereby reduce porphyrin synthesis.
  - **Aspirin** and **paracetamol** are safe in porphyria as well as **gabapentin** (used to control seizure activity).
  - Most other anti-epileptics including BDZ (Dormicum) may exacerbate attacks, as well as metoclopramide and domperidone, so **phenothiazines** should be used to control nausea.
  - Hypertension and hyponatraemia should be corrected due to the increased risk of seizure. en m
- **Stress**, **infection**, **pregnancy**, struation, **OCP**, **starvation** (low carbohydrate intake) and certain **drugs** may precipitate acute attacks.
- In general, **drugs** that lead to **increased activity of the hepatic P450** system, such as phenobarbital, sulphonamides, **oestrogens**, and **alcohol**, are associated with increased risk of acute attacks.

| Drugs which may precipitate attack: | Safe drugs |
|---|---|
| • **Alcohol**<br>• **Benzodiazepines (BDZ)**<br>• **Barbiturates (Thiopentone)**<br>• **Halothane**<br>• **Oral contraceptive pill**<br>• **Sulphonamides**<br>• **Phenytoin** | • Aspirin<br>• Paracetamol<br>• Codeine<br>• Morphine<br>• **Chlorpromazine (Largactil)**<br>• Beta-blockers<br>• Penicillin<br>• Metformin |

**Ibuprofen** is **safe** for use in AIP, but diclofenac should be avoided.

A 43-year-old man presents with known acute intermittent porphyria is brought to the Emergency Department by the police due to an acute psychosis. What is the most suitable drug for sedation? >> **Chlorpromazine (NOT BDZs).**

Use of IV glucose **during an attack** can lead to more rapid resolution of symptoms, as such that would be the favoured first approach. It will have most impact in shortening the duration and severity of symptoms.

**Phenothiazines** may be used for restlessness, nausea and anxiety, and **beta blockers** have a role in the management of sympathetic activation. **Opiates** can be used as analgesics.

**EX**: A **27**-year-old **woman** presents to the ER very **agitated**, complaining of **abdominal pain**. This has been her 3rd **recurrent** attendance over the past 6 months, and each time there have been no significant findings. Her only medication of note is the **oral contraceptive pill** and **oral antihistaminic**.

On this occasion her **BP is elevated 155/90 mmHg**, her pulse is 92, and her **temperature is 37.8°C**. Her abdomen is **generally tender but soft**, and she has active bowel sounds. She complains of **lower limb weakness**, and she appears to have 4/5 power weakness below the knee. Lab: **serum Na 132** mmol/l, **mild leucocytosis**.
The most likely diagnosis is >>> **acute intermittent porphyria (AIP).**

**EX**: A **23**-year-old **woman** presents to the hospital with a **third** attack of **anxiety**, **abdominal pain** and **hypertension** in the last six months.
O/E: BP is 150/80 mmHg, pulse is 95 and regular. She has generalised abdominal pain but her abdomen is soft and she has active bowel sounds, Lab: Serum Na 130 mmol/L >>> **acute intermittent porphyria with SIADH.**

## Porphyria cutanea tarda (PCT)

- Most common hepatic porphyria.
- Defect in **uroporphyrinogen decarboxylase**.
- May be caused by hepatocyte damage e.g. excess **alcohol**, oestrogens and iron.
- Classically **photosensitive rash** with bullae, skin fragility on face and **dorsal aspect of hands.**
- Urine: elevated uroporphyrinogen and pink fluorescence of urine under Wood's lamp.
- **Treatment:**
  - **Withdrawal** of the precipitant.
  - **Venesection** is effective (450 ml/week) until Hb is 120 g/L.
  - **Chloroquine** may also be effective because it promotes porphyrin excretion.

## Variegate porphyria:

- Autosomal dominant.
- Defect in **protoporphyrinogen oxidase.**

- **Characterised by raised faecal porphyrins** (copro-porphyrins and proto-porphyrins).
- It is rarely present with acute episode (unlike AIP).
- **The only reported symptom is photosensitive** blistering rash.
- Abdominal and neurological symptoms
- More common in South Africans

## Fluid therapy

The prescription of intravenous fluids is one of the most common tasks that junior doctors need to do. The typical daily requirement is:

- **1.5 ml/kg/hr. fluid** - for a **80**kg man around 2-3 litres/day
- 70-150mmol sodium
- 40-70mmol potassium

**This is why the typical regime prescribed for patients is**

- **1 litre 5% dextrose** with **20mmol potassium** over 8 hours
- **1 litre 0.9% normal saline** with **20mmol potassium** over 8 hours
- **1 litre 5% dextrose** with **20mmol potassium** over 8 hours

The amount of fluid patients require obviously varies according to their recent and past medical history.

For example a patient who is post-op and is having significant losses from drains will require more fluid whereas a patient with heart failure should be given less fluid to avoid precipitating pulmonary oedema.

The table below shows the electrolyte concentrations (in millimoles/litre) of plasma and the most commonly used fluids:

| | $Na^+$ | $Cl^-$ | $K^+$ | $HCO3^-$ | $Ca^{2+}$ |
|---|---|---|---|---|---|
| **Plasma** | 135-145 | 98-105 | 3.5-5 | 22-28 | 2.3-2.6 |
| **0.9% normal saline** | 150 | 150 | - | - | - |
| **5% dextrose** | - | - | - | - | - |
| **Hartmann's solution** | 131 | 111 | 5 | 29 | 2 |

Understanding sodium requirements is important especially when maintenance intravenous fluid prescriptions are required.

Daily maintenance requirements vary between individuals and the clinical situation, but for **a 70 kg male** the generally accepted requirements per day are:

- **2.5-3.0L water**
- **120-140 mmol sodium (~2 mmol/kg)**
- **70 mmol potassium (~1 mmol/kg)**

**Hartmann's solution** contains **131** mmol **Na per litre**,
**Normal saline** has **150** mmol/L and
**Dextrose saline** has **30** mmol/L.

**Q**: What is their daily requirement of salt? >>>>> **6 gm/day**.
The daily sodium requirement is **70-150mmol**. We can convert this **to mg** by **multiplying by 58.5** (molecular weight of **sodium** is approximately **23**, **chloride** is **35.5**).
So, 70-150mmol = 4095 - 8775mg = 4 - 8.5g. The nearest answer to this is **6g**.
Secondly, this figure ties in with the governments recommended **oral salt intake of 6g/day.**

## Fitness to fly

The **Civil Aviation Authority (CAA)** has issued guidelines on air travel for people with medical conditions; please see the link. ***www.caa.co.uk***

### Cardiovascular disease:

- Unstable angina, uncontrolled hypertension, uncontrolled cardiac arrhythmia, decompensated heart failure, severe symptomatic valvular disease: should not fly.
- Uncomplicated myocardial infarction: may fly after 7-10 days.
- Complicated myocardial infarction: after 4-6 weeks.
- Coronary artery bypass graft: after 10-14 days.
- Percutaneous coronary intervention: after 5 days.

### Respiratory disease:

- Pneumonia: should be 'clinically improved with no residual infection'.
- Pneumothorax: absolute contraindication, the CAA suggest patients may travel 2 weeks after successful drainage if there is no residual air. The British Thoracic Society used to recommend not travelling by air for a period of 6 weeks but this has now been changed to 1 week post check x-ray.

### Pregnancy:

- Most airlines do **not allow** travel **after 36 weeks** for a single pregnancy and **after 32 weeks** for a **multiple** pregnancy.
- Most airlines require a **certificate after 28 weeks** confirming that the pregnancy is progressing normally.

## Surgery:

- Travel should be avoided for 10 days following abdominal surgery
- Laparoscopic surgery: after 24 hours
- Colonoscopy: after 24 hours
- Following the application of a **plaster cast**, the majority of airlines restrict flying for **24 hours** on flights of less than 2 hours or **48 hours** for longer flights this is due to the fact that air may be trapped beneath the cast.

## Haematological disorders:

- Patients with a haemoglobin of greater than **8** g/dl may travel without problems (assuming there is no coexisting condition such as cardiovascular or respiratory disease).

# Vitamin deficiency

| Vitamin | Chemical name | Deficiency state |
|---|---|---|
| **A** | Retinoids | Night-blindness (nyctalopia) |
| **B1** | Thiamine | Beriberi:<br>• Polyneuropathy, Wernicke-Korsakoff syndrome<br>• Heart failure |
| **B2** | (riboflavin) | Angular stomatitis, cheilosis, corneal vascularization |
| **B3** | **Niacin (Nicotinic acid)** | **Pellagra**:<br>• Dermatitis<br>• Diarrhoea<br>• Dementia |
| **B6** | Pyridoxine | Anaemia, irritability, seizures |
| **B7** | Biotin | Dermatitis, seborrhoea |
| **B9** | Folic acid | Megaloblastic anaemia, deficiency during pregnancy - neural tube defects |
| **B12** | Cyanocobalamin | Megaloblastic anaemia, peripheral neuropathy |

| | | |
|---|---|---|
| **C** | Ascorbic acid | **Scurvy:**<br>• Gingivitis<br>• Bleeding<br>• poor wound healing |
| **D** | Ergocalciferol, cholecalciferol | Rickets, osteomalacia |
| **E** | Tocopherol, tocotrienol | Mild haemolytic anaemia in newborn infants, ataxia, peripheral neuropathy |
| **K** | Naphthoquinone | Haemorrhagic disease of the newborn, bleeding diathesis |
| **Selenium** | Selenium | Keshan disease (cardiomyopathy). |

The best source of Vit. D is **Cod liver oil**, it provides about 1,300 IU /15 ml serving.

## Vitamin C (ascorbic acid)

**Vitamin C is a water soluble vitamin.**

### Functions:

- Antioxidant.
- Collagen synthesis: acts as a cofactor for enzymes that are required for the hydroxylation proline and lysine in the synthesis of collagen.
- Facilitates iron absorption.
- Cofactor for norepinephrine synthesis.

Vitamin C deficiency (**scurvy**) leads to defective synthesis of collagen resulting in capillary fragility (bleeding tendency) and poor wound healing.

### Features vitamin C deficiency:

- General malaise.
- **Gingivitis**, loose teeth.
- Bleeding from gums, haematuria, and epistaxis.
- Poor wound healing.

# Vitamin C deficiency (scurvy)

**Vitamin C** (ascorbic acid) is found in citrus fruits, tomatoes, potatoes, Brussel sprouts, cauliflower, broccoli, cabbage and spinach.
Deficiency (commonly called scurvy) leads to impaired collagen synthesis and disordered connective tissue as ascorbic acid is a cofactor for enzymes used in the production of proline and lysine.
It is associated with severe malnutrition as well as drug and alcohol abuse, and those living in poverty with limited access to fruits and vegetables.

## Symptoms and signs include:

- Follicular hyperkeratosis and perifollicular haemorrhage
- Ecchymosis, easy bruising
- **Poor wound healing**
- **Gingivitis** with bleeding and receding gums
- Sjogren's syndrome
- Arthralgia
- Oedema
- Impaired wound healing
- Generalised symptoms such as weakness, malaise, anorexia and depression

# Vitamin B6 (pyridoxine)

Vitamin B6 is a water soluble vitamin of the B complex group. It is converted to pyridoxal phosphate (PLP) which is a cofactor for many reactions including transamination, deamination and decarboxylation.

## Causes of vitamin B6 deficiency

- isoniazid therapy

## Consequences of vitamin B6 deficiency

- peripheral neuropathy
- sideroblastic anemia

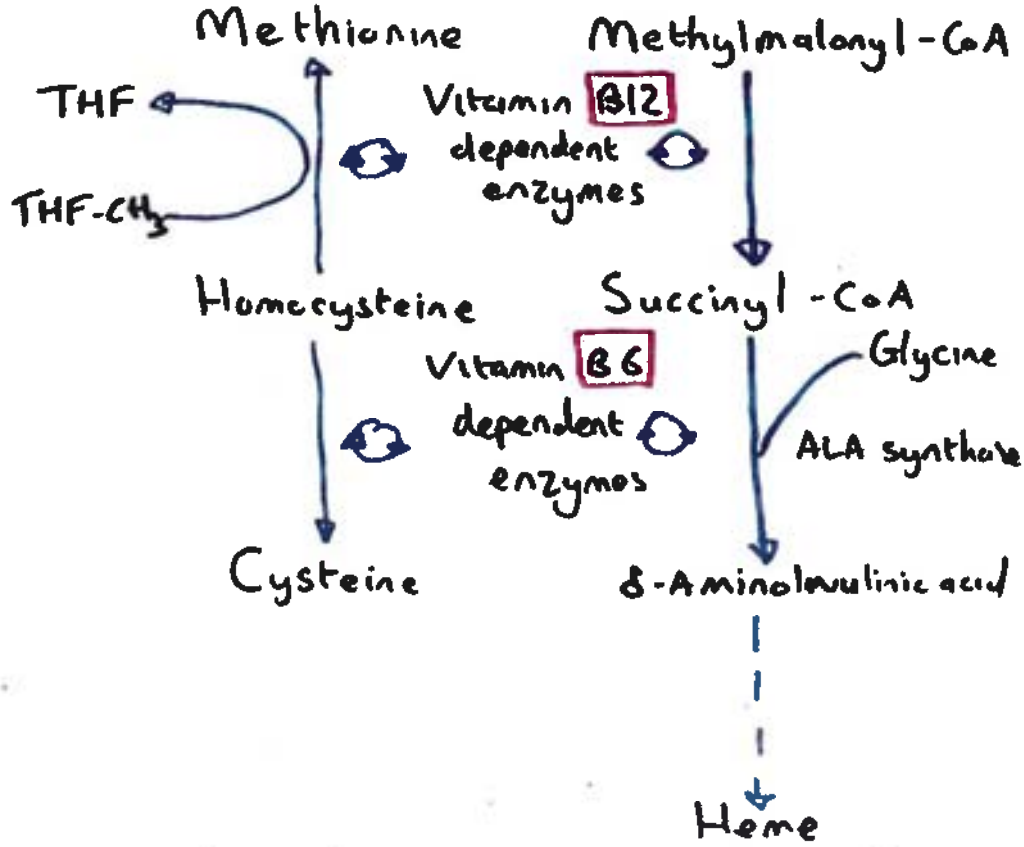



Diagram showing the biochemical role of vitamin B12 and vitamin B6

# Vitamin B12 deficiency

Vitamin B12 is mainly used in the body for red blood cell development and also maintenance of the nervous system.

It is **absorbed after binding to intrinsic factor I.F.** (secreted from **parietal cells** in the stomach) and is **actively absorbed in the terminal ileum**.

A **small** amount of vitamin B12 is **passively** absorbed **without being bound** to intrinsic factor.

Vitamin B12 >>>> is **actively** absorbed in the **terminal ileum by IF**.

## Causes of vitamin B12 deficiency:

- Pernicious anaemia
- Post **gastrectomy**
- Poor diet
- Disorders of **terminal ileum** (site of absorption): Crohn's, blind-loop etc

## Features of vitamin B12 deficiency:

- Macrocytic anaemia
- Sore tongue and mouth
- Neuropsychiatric symptoms: e.g. Ataxia and Mood disturbances

## Management:

- If no neurological involvement **1 mg of IM Hydroxocobalamin 3 times each week for 2 weeks, then once every 3 months.**
- If a patient is also deficient in **folic acid then it is important to treat the B12 deficiency first** to avoid precipitating subacute combined degeneration (SCD) of the cord.

**MRCP part 1 exam: Which structure in the body are able to synthesize vitamin B12?**

>> **gut bacteria**

- It is synthesized by gut bacteria in humans, but humans cannot absorb the $B_{12}$ made in their guts, as it is made in the colon which is too far from the small intestine, where absorption of $B_{12}$ occurs
- Therefore diet is the only source of vit B12.

# Vitamin B1 (thiamine)

Thiamine is a water soluble vitamin of the B complex group.
One of it's phosphate derivates, thiamine pyrophosphate (TPP), is a coenzyme in the following enzymatic reactions:

- pyruvate **dehydrogenase** complex
- pyruvate **decarboxylase** in ethanol fermentation
- alpha-ketoglutarate dehydrogenase complex
- branched-chain amino acid **dehydrogenase** complex
- 2-hydroxyphytanoyl-CoA lyase
- transketolase

Thiamine is therefore important in the catabolism of sugars and aminoacids. The clinical consequences of thiamine deficiency are therefore seen first in highly aerobic tissues such as the brain (Wenicke-Korsakoff syndrome) and the heart (wet beriberi).

## Causes of thiamine deficiency:

- alcohol excess. Thiamine supplements are the only routinely recommend supplement in patients with alcoholism
- malnutrition

## Conditions associated with thiamine deficiency:

- **Wernicke's encephalopathy: nystagmus, ophthalmoplegia and ataxia**
- Korsakoff's syndrome: amnesia, confabulation
- **dry beriberi: peripheral neuropathy**
- **wet beriberi: dilated cardiomyopathy**

**What happens if you do not give the thiamine first before starting an intravenous glucose infusion?**

- ATP failing to be adequately generated,
- The inability of pyruvate to enter the TCA cycle >> accumulate of pyruvate >> pyruvate convert to lactate in order to be able to maintain glycolysis. ↑**acidosis.**
- **inability of the pentose phosphate pathway to protect the cell from reactive oxygen species** that damage cellular structures, results in either **cell death or activation of apoptosis.**

**Vitamin function as a co-factors:**

- Biotin for carboxylase reactions.
- **Thiamine for dehydrogenase reactions**
- B9 (folate) for transferases.
- Vit C for hydroxylases.

# Vitamin E deficiency

**Active form: tocopherol Function**

- Lipid-soluble antioxidant in the glutathione peroxidase pathway >> removes the free radical intermediates >> protects cell membranes from oxidation by reacting with lipid radicals produced in the lipid peroxidation chain reaction.

**Therapeutic uses** >> Nonalcoholic steatohepatitis

## Features

- **Neurologic dysfunction**
  - Demyelination of the posterior column and spinocerebellar tract >> ↓ proprioception and vibration sensation; ataxia
  - Neurologic symptoms are similar to vitamin B12 deficiency, except that vitamin E deficiency does not lead to hypersegmented neutrophils, megaloblastic anemia, and increased methylmalonic acid levels.
- **Hemolytic anemia;** increased fragility of erythrocytes and membrane breakdown
- **Acanthocytosis**
- **Muscle weakness**

## Hypervitaminosis E

- **interfere with vitamin K metabolism >> vitamin K deficiency >> increased tendency to bleed.**

# Vitamin K

Vitamin K is a fat-soluble vitamin which acts as a cofactor in the carboxylation of clotting **factors (II, VII, IX, X).**

## Clinically, it is used to reverse the effects of warfarinisation

- takes up to 4 hours for there to be a change in the INR

## Vitamin K deficiency

- as it is fat-soluble, vitamin K levels may fall in conditions affecting fat absorption
- deficiency may also occur after prolonged use of broad-spectrum antibiotics by eliminating the gut flora

# Vitamin A

**Active forms:** Retinal and Retinoic acid

## Sources

- Plant sources; yellow and leafy vegetables
- Animal sources: in storage form; liver

## Causes

- Disorders associated with fat malabsorption: inflammatory bowel disease (e.g., Crohn disease), celiac disease, cystic fibrosis, pancreatic insufficiency

## Features

### Ocular manifestations

- Night blindness (nyctalopia)
- Xerophthalmia
- Keratomalacia
- Bitot spots: gray, triangular, dry patches on the bulbar conjunctiva, covered by a layer with a foamy appearance
  - Typical sign of vitamin A deficiency
  - Caused by squamous cell metaplasia and keratinization of the conjunctiva

**Keratinizing** squamous metaplasia of the bladder (pearl-like plaques on cystoscopy)

**Xerosis** cutis (dry skin)

**Immunosuppression**

## Vitamin A toxicity

- Causes: increased intake via supplements or drugs
- Acute toxicity: Nausea, vomiting, Vertigo, Blurred vision
- Chronic toxicity:
  - Alopecia, Dry skin, scaling
  - Arthralgias
  - Hepatosplenomegaly, hepatic toxicity
  - Pseudotumor cerebri

**Which substances in vitamin A is most likely to be maximally involved in correcting the visual disturbance?**

- Retinaldehyde
- Retinaldehyde is derived from the oxidation of retinol

**What would you give the patient who taking long term steroids to help his wound heal faster?**

**>> Vitamin A**

- Vitamin A is believed to counteract the effect of steroids on slowing woundhealing by stimulating TGF-beta and IGF-1, as well as collagen production. However, high levels (which can accumulate because vitamin A is fat soluble) can also be toxic and inhibit colla en s nthesis, such as in the skin.

## Folate metabolism

The best source of food for folic acid >>>> **Liver**, green vegetables and nuts.

### Drugs which interfere with metabolism:

- Trimethoprim
- Methotrexate
- Pyrimethamine

### Drugs which can reduce absorption:

- Phenytoin

## Pyruvate kinase

- **Pyruvate kinase is the rate-limiting step in glycolysis** and gluconeogenesis
- It catalyses the transfer of a phosphate group from phosphoenolpyruvate to ADP, yielding a molecule of pyruvate and a molecule of ATP
- **Deficient pyruvate kinase activity may result in the development of hereditary haemolytic anaemias**

**Which biochemical processes is likely to contribute most to energy creation in long distance running?**

**>> Fatty acid oxidation**

## Pellagra

It is characterized by **4Ds**: **Dementia**, **Diarrhoea**, **Dermatitis** and **Death**.

The rash is photosensitive and normally affects the face, neck and forearm.

It is rare and can be **primary** or **secondary**.

**Primary** causes include **niacin** or tryptophan (precursor of niacin) deficiency.
**Secondary** caused include:

- **Carcinoid syndrome**, as the tumour cells convert tryptophan to serotonin, therefore reducing endogenous niacin production.
- **Chronic alcoholism.**
- Anorexia nervosa.
- GIT TB.
- HIV.

Patients usually develop **right-sided valvular disease** >>> Echo: **tricuspid regurgitation** and **pulmonary stenosis**.

## Classification of haemorrhage

| Parameter | I | II | III | IV |
|---|---|---|---|---|
| **Blood loss (ml)** | <750 | 750-1500 | 1500-2000 | >2000 |
| **Blood loss (%)** | <15% | 15-30% | 30-40% | >40% |
| **Pulse rate (beats/min)** | <100 | >100 | >120 | >140 |
| **Blood pressure** | Normal | Decreased | Decreased | Decreased |
| **Respiratory rate (breaths/min)** | 14-20 | 20-30 | 30-40 | >35 |
| **Urine output (ml/hour)** | >30 | 20-30 | 5-15 | Negligible |
| **CNS symptoms** | Normal | Anxious | Confused | Lethargic |

## Malignant hyperpyrexia (MH)

Malignant hyperpyrexia (MH) is characterised by increased temperature and muscle rigidity **during anaesthesia**, which results from abnormal skeletal muscle contraction and increased metabolism.

The predisposing gene is thought to be on **chromosome 19**, close to the gene for the ryanodine/dihydropyridine receptor complex.

Known triggering agents include the volatile anaesthetic agents and **suxamethonium**. Patients show different sensitivity to the triggering agents and the reaction can be delayed by several hours.

**Intravenous dantrolene (up to 10 mg/kg)** is the **only available specific ttt** and care must be taken when administering as **the solution has a pH of 9-10**.

The **prognosis** of malignant hyperpyrexia is **good** when the appropriate treatment is instigated early, **mortality** being **less than 5%** (prior to dantrolene the mortality was 80%).

Serum creatine kinase elevation and myoglobinuria are **suggestive** but **not diagnostic** of MH. Myoglobin and creatine kinase are both known to increase after giving suxamethonium to normal patients.

Contracture tests using caffeine and halothane are the investigations of choice.

Muscle **biopsies** may appear histologically **normal**.

## Hiccup

Hiccup is caused by frequent or **rhythmic clonic contraction** of the **diaphragm**.

**When prolonged, other causes should be considered including:**

- **CNS** disease - **posterior fossa tumour**, brain injury, encephalitis
- **Phrenic nerve** or **diaphragm irritation** - tumour, pleurisy, pneumonia, intrathoracic adenopathy, pericarditis, GERD.
- **Systemic** causes include **alcohol** intoxication and **uraemia**.
- **Other** causes include **foreign body or insect in the ear**. In infants it may be associated with apnoea or hyperventilation.

Folk remedies include aerophagia, breath holding, pharyngeal stimulation, distraction.
Haloperidol, metoclopramide and several anaesthetic agents are also said to work.

# Ophthalomolgy

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# Blepharitis

- Blepharitis is inflammation of the eyelid margins.
- It may due to either **meibomian** gland dysfunction (common, posterior Blepharitis) or **seborrhoeic dermatitis/staphylococcal** infection (less common, anterior Blepharitis).
- Blepharitis is also more common in patients with **acne rosacea**.
- The meibomian glands secrete oil on to the eye surface to prevent rapid evaporation of the tear film.
- Any problem affecting the meibomian glands (as in blepharitis) can hence cause drying of the eyes which in turns leads to irritation.

## Features:

- Symptoms are usually **bilateral**
- Grittiness and discomfort, particularly around the eyelid margins
- Eyes may be sticky in the morning
- Eyelid margins may be red. **Swollen eyelids may be seen in staphylococcal blepharitis**
- Styes and chalazions are more common in patients with blepharitis.
- Secondary conjunctivitis may occur

## Management:

- Softening of the lid margin using **hot compresses** twice a day.
- **Mechanical removal of the debris from lid margins** - cotton wool buds dipped in a mixture of cooled boiled water and baby shampoo is often used, an alternative is sodium bicarbonate, a teaspoonful in a cup of cooled water that has recently been boiled
- **Artificial tears** may be given for symptom relief in people with dry eyes or an abnormal tear film.
- **Topical Antibiotic Eye drops** if swollen eyelids.

## Ptosis

Ptosis may be unilateral or bilateral.

| Causes of bilateral ptosis: | Causes of unilateral ptosis, as bilateral causes plus: |
|---|---|
| ➢ **Myotonic dystrophy.**<br>➢ **Myasthenia gravis**<br>➢ **Syphilis.**<br>➢ Congenital. | ➢ **Horner's**<br>➢ **Third nerve palsy** |

*Ptosis is much more common in myasthenia gravis than Lambert-Eaton syndrome

## Lacrimal duct problems

**Dacryocystitis** is infection of the lacrimal sac.

**Features:**

- **Watering eye (epiphora)**
- **Swelling** and **erythema** at the **inner canthus of the eye**

**Management** is with systemic antibiotics. Intravenous antibiotics are indicated if there is associated periorbital cellulitis.

**Congenital lacrimal duct obstruction** affects around 5-10% of newborns. It is bilateral in around 20% of cases.

**Features:**

- Watering eye (even if not crying)
- Secondary infection may occur
- Symptoms resolve in 99% of cases by 12 months of age.

## Thyroid eye disease

Thyroid eye disease affects between **25-50%** of patients with **Graves'** disease.

### Pathophysiology:

- It is thought to be caused by an autoimmune response against an autoantigen, possibly the **TSH receptor** → retro-orbital inflammation.
- The inflammation results in glycosaminoglycan and collagen deposition in the muscles.

## Prevention (Avoid):

- **Smoking** is the **most important modifiable risk factor** for the development of thyroid eye disease.
- **Radioiodine treatment** may **increase** the inflammatory symptoms seen in thyroid eye disease. In a recent study of patients with Graves' disease around 15% developed, or had worsening of, eye disease. Prednisolone may help reduce the risk.

## Features:

- The patient may be eu-, hypo- or hyperthyroid at the time of presentation
- Exophthalmos
- Conjunctival oedema
- Optic disc swelling
- Ophthalmoplegia
- Inability to close the eye lids may lead to sore, dry eyes.
- If **severe** and **untreated** patients can be at risk of >> **exposure keratopathy (Eye is red, painful and ↓ V/A).**

## Management:

- Topical lubricants: to prevent corneal inflammation caused by exposure.
- Steroids.
- Radiotherapy.
- Surgery.

**Monitoring patients with established thyroid eye disease:** For patients with established thyroid eye disease the following symptoms/signs should indicate the need for **urgent review by an ophthalmologist:**

- **Unexplained deterioration in vision**
- **Awareness of change in intensity or quality of colour vision** in one or both eyes
- History of eye suddenly 'popping out' **(globe subluxation)**
- Obvious **corneal opacity**
- **Cornea still visible** when the eyelids are closed
- **Disc swelling**

# Red eye

There are many possible causes of a red eye.
It is important to be able to recognise the causes which require urgent referral to an ophthalmologist.
Below is a brief summary of the key distinguishing features

**Acute angle closure glaucoma**

- severe pain (may be ocular or headache)
- decreased visual acuity, patient sees haloes
- **semi-dilated pupil**
- hazy cornea

**Anterior uveitis**

- acute onset
- pain
- blurred vision and photophobia
- **small, fixed oval pupil, ciliary flush**

**Scleritis**

- severe pain (may be worse on movement) and tenderness
- may be underlying autoimmune disease e.g. rheumatoid arthritis

**Conjunctivitis**

- purulent discharge if bacterial, clear discharge if viral

**Subconjunctival haemorrhage**

- history of trauma or coughing bouts

**Endophthalmitis**

- typically, red eye, pain and visual loss following intraocular surgery

# Conjunctivitis

purulent discharge if bacterial, clear discharge if viral

## Viral conjunctivitis

- causes redness, soreness and watering.
- In severe cases it can cause a keratitis which may affect vision.
- It is highly contagious so patients should be advised to practise strict hand hygiene, to avoid sharing towels and to take time off work.
- It is a self-limiting disease which may take several weeks to resolve.
- Patients are treated with topical lubricants and some ophthalmologists give topical chloramphenicol to protect against secondary bacterial infections.

## Subconjunctival haemorrhage

- history of trauma or coughing bouts
- adverse effect of aspirin therapy (and other antiplatelets).
- It usually resolves over 10-14 days.
- If the haematoma is large it may be worth considering prophylactic antibiotic eyedrops.

## Keratitis

Keratitis describes inflammation of the cornea.
Microbial keratitis is not like conjunctivitis - it is potentially sight threatening and should therefore be urgently evaluated and treated.
This is characterised by dendritic ulcers. Rarer forms involve the stroma or endothelium.

### Aetiology

#### Causes

- **bacterial**
  - typically, Staphylococcus aureus
  - Pseudomonas aeruginosa is seen in contact lens wearers
- **fungal**
- **amoebic**
  - acanthamoebic keratitis
  - accounts for around 5% of cases
  - increased incidence if eye exposure to soil or contaminated water
  - pain is classically out of proportion to the findings
- **parasitic:** onchocercal keratitis ('river blindness')

**Remember, other factors may causes keratitis**:

- viral: herpes simplex keratitis
- environmental
  - photokeratitis: e.g. welder's arc eye
  - exposure keratitis
  - contact lens acute red eye (CLARE)

### Clinical features

#### Features

- red eye: pain and erythema
- photophobia
- foreign body, gritty sensation
- hypopyon may be seen

## Evaluation and management

### Referral

- contact lens wearers
  - assessing contact lens wearers who present with a painful red eye is difficult
  - an accurate diagnosis can only usually be made with a slit-lamp, meaning same-day referral to an eye specialist is usually required to rule out microbial keratitis

### Management

- stop using contact lens until the symptoms have fully resolved
- topical antibiotics
  - typically, quinolones are used first-line
- cycloplegic for pain relief
  - e.g. cyclopentolate

### Complications may include:

- corneal scarring
- perforation
- endophthalmitis
- visual loss

# Herpes simplex keratitis

Herpes simplex keratitis most commonly presents with a dendritic corneal ulcer.

## Features

- red, painful eye
- photophobia
- epiphora
- visual acuity may be decreased
- fluorescein staining may show an epithelial ulcer

## Management

- immediate referral to an ophthalmologist
- topical aciclovir

## Herpes zoster ophthalmicus

Herpes zoster ophthalmicus (HZO) describes the reactivation of the varicella-zoster virus in the area supplied by the ophthalmic division of the trigeminal nerve. It accounts for around 10% of case of shingles.

### Features

- vesicular rash around the eye, which may or may not involve the actual eye itself
- Hutchinson's sign: rash on the tip or side of the nose. Indicates nasociliary involvement and is a strong risk factor for ocular involvement

### Management

- **oral antiviral** treatment for 7-10 days
  - ideally started within 72 hours
  - intravenous antivirals may be given for very severe infection or if the patient is immunocompromised
  - **topical antiviral treatment is not given in HZO**
- topical corticosteroids may be used to treat any secondary inflammation of the eye
- ocular involvement requires urgent ophthalmology review

### Complications

- ocular: conjunctivitis, keratitis, episcleritis, anterior uveitis
- ptosis
- post-herpetic neuralgia.

## Scleritis

### Definition

inflammation that occurs throughout the entire thickness of the sclera,

### Aetiology

may be underlying autoimmune disease e.g. rheumatoid arthritis

- Around 50% of patients with scleritis have an underlying disease, of which the majority are connective tissue disorders.
- **Rheumatoid arthritis is the most common.**

### Features

- **severe pain** (may be worse on movement) and tenderness
  - **pain** in scleritis is more evident and severe than episcleritis.

  - **Tenderness** to palpation of the globe can differentiate it from episcleritis. After asking the patient to look down with eyelids closed, the physician gently presses the globe. Patients with scleritis have tenderness on palpation, while those with episcleritis do not.
  - Unlike scleritis, patients with episcleritis do not complain of **blurred vision or photophobia.**
  - Studies have shown that patients with RA-associated scleritis have **more widespread systemic disease** and a higher mortality rate than those episcleritis.
- 50% of cases are bilateral.
- Pain often radiates to the forehead, brow and jaw. This pain worsens with movement of the eye, and is classically worse at night.
- There is associated watering, photophobia and a gradual decrease in vision (sometimes with diplopia).
- Systemic symptoms such as fever, headache and vomiting can occur.
- On examination the globe is tender, and the sclera can have a bluish tinge.
- visual acuity is normal
- there is marked dilatation of the **deep and superficial** scleral vessels.
- Scleritis may cause thinning of the sclera (**scleromalacia**) and subsequent perforation.

## Treatment

- Management ultimately depends on the underlying cause, but includes NSAIDs and prednisolone.
- **The patient should be referred urgently to the ophthalmology clinic**
  **Application of topical phenylephrine 2.5% leads to blanching of episcleral vessels in episcleritis but not in scleritis.**

# Episcleritis

**Scleritis is painful, episcleritis is not painful**

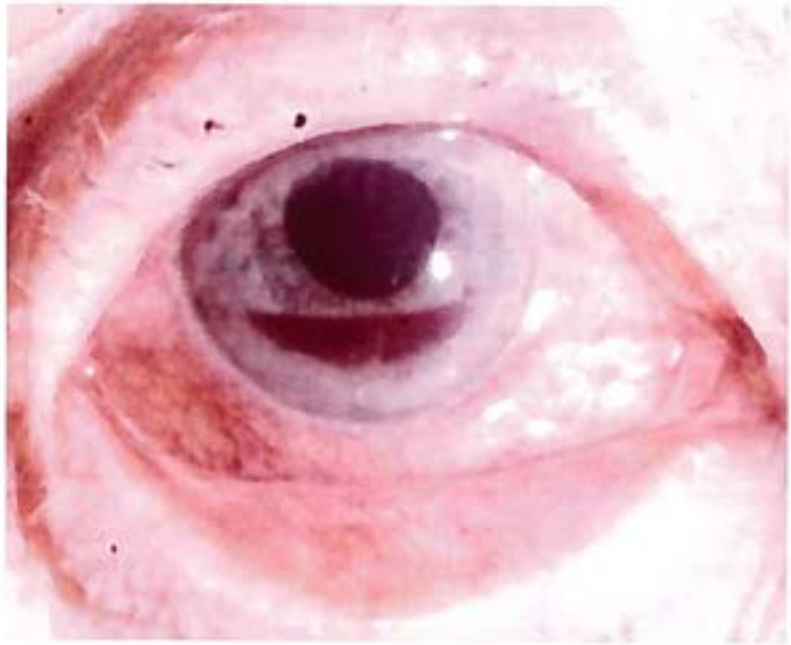
- Results in ocular irritation with nodules.
- acute in onset, with **mild pain** or discomfort / grittiness.
- can be unilateral or bilateral, with localised or diffuse red eye.
- There may be **mild** photophobia and watering. **The lack of photophobia and discharge, and normal vision, makes episcleritis the most likely option**

# Hyphaema

- Occurs when bleeding from iris vessels fills the anterior chamber with blood and if there is enough blood
- the main risk in the acute stage is of raised intraocular pressure (IOP).
- It is usually caused by trauma - often small objects (champagne corks, squash balls) hitting the eye.

## Treatment

- Strict rest is vital if a hyphaema is present, as there is an increased risk of a second bleed in the initial period.
- **Intravenous carbonic anhydrase inhibitors is the most appropriate treatment**
- Aspiration may be required to prevent loss of vision.
- avoid drops that dilate the pupil (such as anticholinergics) the iris remains stable and a second bleed is therefore less likely.



hyphaema: blood in the anterior chamber.

## Band keratopathy

- It is a corneal disease derived from the appearance of calcium on the central cornea caused by **calcium deposition in bowman's layer**.
- This is an example of **metastatic calcification**, which by definition, occurs in the presence of **hypercalcaemia**.
- **Symptoms:** Pain and ↓ visual acuity.
- **Treatment:** the calcium can be scraped off the cornea or removed with a laser. This can restore sight, but it can take a number of months for normal vision to return as the cornea will be damaged during operation. This can't be repeated too many times as it would make the cornea thinner and thinner.

## Cataracts

### Causes

| Majority | Systemic | Ocular |
|---|---|---|
| • **Aging**<br>• **UV light** | • **DM**<br>• **Steroids**<br>• Infection (**congenital rubella**)<br>• **Metabolic**<br>  ○ diabetes<br>  ○ **Hypocalcaemia**<br>  ○ **Galactosaemia**<br>• **Myotonic dystrophy**<br>• **Down's** syndrome | • **Trauma**<br>• **Uveitis**<br>• High **myopia**<br>• Topical steroids |

### Feature

- **Symptoms:** painless, progressive, and slow vision loss
- **Physical exam:** absent red reflex

### Classification:

- **Nuclear**: change lens refractive index, **common in old age**
- **Polar**: localized, commonly inherited, lie in the visual axis
- **Subscapular**: due to **steroid use**, just deep to the lens capsule, in the visual axis
- **Dot opacities**: common in normal lenses, also seen in diabetes and myotonic dystrophy

## Homocystinuria

Homocystinuria is a **rare autosomal recessive** disease caused by **deficiency of cystathionine beta synthase.**
This results in an accumulation of homocysteine which is then oxidized to homocystine.

### Features:

- Often patients have fine, fair hair
- Musculoskeletal: may be **similar to Marfan's** - Arachnodactyly etc.
- **Neurological** patients may have **learning difficulties**, seizures.
- Ocular: **Downwards** (**Inferonasal**) **dislocation** of **lens**
- ↑ **risk of arterial and venous thromboembolism**
- Also malar flush, livedo reticularis

**Diagnosis** is made by the **cyanide-nitroprusside test**, which is also positive in cystinuria.

**Treatment** is supplementation of **vitamin B6 (pyridoxine)**.

**Marfan's syndrome >>> Upwards lens dislocation (Superotemporal ectopia lentis)**
While, **Homocystinuria >>> Downwards (Inferonasal) dislocation of lens.**

## Marfan's syndrome

Marfan's syndrome is an **autosomal dominant** connective tissue disorder.

It is caused by a defect in the **fibrillin-1 gene** on **chromosome 15** and affects **around 1 in 3,000 people**.

### Features:

- Tall stature with arm span to height ratio > 1.05
- High-arched palate
- Arachnodactyly
- Pectus excavatum
- Pes planus
- Scoliosis of > 20 degrees
- Heart: **dilation of the aortic sinuses (seen in 90%)** which may lead to aortic aneurysm, aortic dissection, aortic regurgitation, **mitral valve prolapse (75%).**

- Lungs: repeated pneumothoraxes
- Eyes: **Upwards lens dislocation** (**Superotemporal ectopia lentis**) which seen in around **50%** of patients, **blue sclera**, **and myopia.**
- Dural ectasia (ballooning of the dural sac at the lumbosacral level)

The life expectancy of patients used to be around 40-50 years.

With the advent of regular echocardiography monitoring and beta-blocker/ACE-inhibitor therapy this has improved significantly over recent years.

Aortic dissection and other cardiovascular problems remain the leading cause of death however.

## Ectopia lentis

**Ectopia lentis/subluxation of the lens is associated with:**

- Ehlers-Danlos syndrome
- Marfan's syndrome
- Weill-Marchesani syndrome (short stature, skeletal abnormalities and ectopia lentis), and
- Refsum's disease.

## Glucoma

- Glaucoma is a group of disorders characterized by optic neuropathy due, in the majority of patients, to raised intraocular pressure (IOP).
- It is now recognized that a minority of patients with raised IOP do not have glaucoma and vice versa.

## Acute angle closure glaucoma

In acute angle-closure glaucoma (AACG) there is a rise in IOP secondary to an impairment of aqueous outflow. Factors predisposing to AACG include:

- hypermetropia (long-sightedness)
- pupillary dilatation
- lens growth associated with age
- **neovascular glaucoma** (new blood vessels grow into the angle of the eye and block the aqueous outflow). **Vascular endothelial growth factor (VEGF)** is a growth factor protein that works by stimulating angiogenesis. Hence, inhibiting VEGF (e.g. Bevacizumab) can stop the progression of neovascularization.

## Diagnosis

- Tonometry: >> Elevated IOP (> 21 mm Hg)
- Gonioscopy: the gold-standard diagnostic test >> Narrowing/closure of the iridocorneal angle.

## Features

- severe pain: may be ocular or headache
- decreased visual acuity
- symptoms worse with mydriasis (e.g. watching TV in a dark room)
- hard, red-eye
- haloes around lights
- semi-dilated non-reacting pupil
- corneal oedema results in dull or hazy cornea
- systemic upset may be seen, such as nausea and vomiting and even abdominal pain

## Management

The management of AACG is an emergency and should prompt urgent referral to an ophthalmologist.

Emergency medical treatment is required to lower the IOP with more definitive surgical treatment given once the acute attack has settled.

**There are no guidelines for the initial medical treatment emergency treatment. An example regime would be:**

- combination of eye drops, for example:
  - a direct parasympathomimetic (e.g. pilocarpine, causes contraction of the ciliary muscle → opening the trabecular meshwork → increased outflow of the aqueous humour)
  - a beta-blocker (e.g. timolol, decreases aqueous humour production)
  - an alpha-2 agonist (e.g. apraclonidine, dual mechanism, decreasing aqueous humour production and increasing uveoscleral outflow)
- intravenous acetazolamide
  - reduces aqueous secretions

## Definitive management

- laser peripheral iridotomy
  - creates a tiny hole in the peripheral iris → aqueous humour flowing to the angle
  - Anti-VGF

# Primary open-angle glaucoma

## presentation and diagnosis

Glaucomas are optic neuropathies associated with raised intraocular pressure (IOP). They can be classified based on whether the peripheral iris is covering the trabecular meshwork, which is important in the drainage of aqueous humour from the anterior chamber of the eye.

In primary open-angle glaucoma (POAG), the iris is clear of the meshwork. The trabecular network functionally offers an increased resistance to aqueous outflow, causing increased IOP.

It is now recognised that a minority of patients with raised IOP do not have glaucoma and vice versa.

## Risk factors:

- increasing age
  - affects < 1'5 in individuals under 55 years of age
  - but up to 10% over the age of 80 years
- genetics
  - first degree relatives of an open-angle glaucoma patient have a 16% chance of developing the disease
- Afro Caribbean ethnicity
- myopia
- hypertension
- diabetes mellitus
- corticosteroids

POAG may present insidiously and for this reason is often detected during routine optometry appointments.

## Features may include

- **peripheral visual field loss - nasal scotomas progressing to 'tunnel vision'**
- decreased visual acuity
- optic disc cupping

## Fundoscopy signs of POAG

1. Optic disc cupping - cup-to-disc ratio >0.7 (normal = 0.4-0.7), occurs as loss of disc substance makes optic cup widen and deepen
2. Optic disc pallor - indicating optic atrophy
3. Bayonetting of vessels - vessels have breaks as they disappear into the deep cup and re-appear at the base

4. Additional features - Cup notching (usually inferior where vessels enter disc), Disc haemorrhages

## Diagnosis:

- Case finding and provisional diagnosis is done by an optometrist
- Referral to the ophthalmologist is done via the GP
- Final diagnosis is done by investigations as below

## Investigations:

- automated perimetry to assess visual field
- slit lamp examination with pupil dilatation to assess optic nerve and fundus for a baseline
- applanation tonometry to measure IOP
- central corneal thickness measurement
- gonioscopy to assess peripheral anterior chamber configuration and depth
- Assess risk of future visual impairment, using risk factors such as IOP, central corneal thickness (CCT), family history, life expectancy

## Management

The majority of patients with primary open-angle glaucoma are managed with eye drops. These aim to lower intra-ocular pressure which in turn has been shown to prevent progressive loss of visual field.

## NICE guidelines:

- first line: prostaglandin analogue (PGA) eyedrop
- second line: beta-blocker, **carbonic anhydrase inhibitor**, or sympathomimetic eyedrop
- if more advanced: surgery or laser treatment can be tried[2]

## Reassessment

- important to exclude progression and visual field loss
- needs to be done more frequently if: IOP uncontrolled, the patient is high risk, or there is progression

| Medication | Mode of action | Notes |
|---|---|---|
| Prostaglandin analogues (e.g. latanoprost) | Increases uveoscleral outflow | Once daily administration<br><br>Preferred first-line therapy. should be used first-line in patients with a history of asthma.<br>**Adverse effects:**<br>• brown pigmentation of the iris,<br>• growth of eyelashes<br>• Epithelial keratopathy<br>• Systemic: paresthesia, hypokalemia, renal stones, acidosis. and aolastic anemia. |
| Beta-blockers (e.g. timolol, betaxolol) | Reduces aqueous production | Should be avoided in asthmatics and patients with heart block |
| Sympathomimetics (e.g. brimonidine, an alpha2-adrenoceptor agonist) | Reduces aqueous production and increases outflow | Avoid if taking MAOI or tricyclic antidepressants<br><br>Adverse effects include hyperaemia |
| Carbonic anhydrase inhibitors (e.g. Dorzolamide) | Reduces aqueous production | Systemic absorption may cause sulphonamide-like reactions |
| Miotics (e.g. pilocarpine, a muscarinic receptor agonist) | Increases uveoscleral outflow | Adverse effects included a constricted pupil, headache and blurred vision |

Surgery in the form of a trabeculectomy may be considered in refractory cases.

## Tunnel vision

Tunnel vision is the concentric diminution of the visual fields

### Causes

- papilloedema
- glaucoma
- retinitis pigmentosa
- choroidoretinitis
- optic atrophy secondary to tabes dorsalis
- hysteria

# Optic atrophy

Optic atrophy is seen as pale, well demarcated disc on fundoscopy.
It is usually bilateral and causes a gradual loss of vision*. Causes may be acquired or congenital

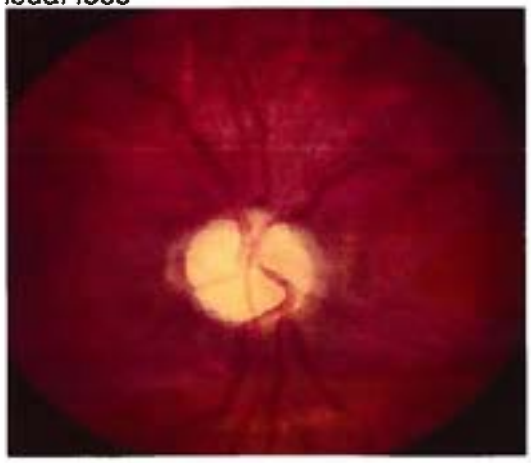
## Acquired causes

- multiple sclerosis
- papilloedema (longstanding)
- raised intraocular pressure (e.g. glaucoma, tumour)
- retinal damage (e.g. choroiditis, retinitis pigmentosa)
- ischaemia
- toxins: tobacco amblyopia, quinine, methanol, arsenic, lead
- nutritional: vitamin B1, B2, B6 and B12 deficiency

## Congenital causes

- Friedreich's ataxia
- mitochondrial disorders e.g. Leber's optic atrophy
- DIDMOAD - the association of cranial Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy and Deafness (also known as Wolfram's syndrome)

*strictly speaking optic atrophy is a descriptive term, it is the optic neuropathy that results in visual loss



**This patient has optic atrophy as revealed by a particularly pale disc.**
**Causes include:**

- Glaucoma
- External compression of the optic nerves, for example, pituitary tumour, and
  Multiple sclerosis

## Anterior uveitis

Anterior uveitis is one of the important differentials of a red eye.
It is also referred to as iritis. Anterior uveitis describes inflammation of the anterior portion of the uvea - iris and ciliary body.
It is associated with HLA-B27 and may be seen in association with other HLA-B27 linked conditions (see below).

### Features

- acute onset
- ocular discomfort & pain (may increase with use)
- pupil may be small +/- irregular due to sphincter muscle contraction
- photophobia (often intense)
- blurred vision
- red eye
- lacrimation
- ciliary flush: a ring of red spreading outwards
- hypopyon; describes pus and inflammatory cells in the anterior chamber, often resulting in a visible fluid level
- visual acuity initially normal → impaired

### Associated conditions

- ankylosing spondylitis
- reactive arthritis
- ulcerative colitis, Crohn's disease
- Behcet's disease
- sarcoidosis: bilateral disease may be seen

### Management

- urgent review by ophthalmology
- cycloplegics (dilates the pupil which helps to relieve pain and photophobia) e.g. Atropine, cyclopentolate
- steroid eye drops

## Posterior uveitis

Posterior uveitis describes inflammation of the choroid, which can involve the retinal vessels.
presents with gradual visual loss and floaters, which is often bilateral.
Discomfort and erythema are rare.
Slit light examination can demonstrate inflammatory lesions on the retina or choroid, with inflammation of the retinal vessels and oedema of the optic nerve.

# Diabetic retinopathy

Diabetic retinopathy is the most common cause of blindness in adults aged 35-65 years-old.

## Pathophysiology

- Hyperglycemia is thought to cause increased retinal blood flow and abnormal metabolism in the retinal vessel walls.
- This precipitates damage to endothelial cells and pericytes
- Endothelial dysfunction leads to increased vascular permeability which causes the characteristic exudates seen on fundoscopy.
- Pericyte dysfunction predisposes to the formation of microaneurysms. Neovasculization is thought to be caused by the production of growth factors in response to retinal ischaemia

## Classification

- Patients are typically classified into those with non-proliferative diabetic retinopathy (NPDR), proliferative retinopathy (PDR) and maculopathy.

## Non-proliferative diabetic retinopathy

**Mild NPDR**

- 1 or more microaneurysm

**Moderate NPDR**

- microaneurysms
- blot haemorrhages
- hard exudates
- cotton wool spots ('soft exudates' - represent areas of retinal infarction), venous beading/looping and intraretinal microvascular abnormalities (IRMA) less severe than in severe NPDR

**Severe NPDR**

- blot hemorrhages and microaneurysms in 4 quadrants
- venous beading in at least 2 quadrants
- IRMA in at least 1 quadrant

## Proliferative diabetic retinopathy

**Key features**

- retinal neovascularisation - may lead to vitrous haemorrhage
- fibrous tissue forming anterior to retinal disc
- more common in Type I DM, 50% blind in 5 years

## Maculopathy

**Key features**

- based on location rather than severity, anything is potentially serious
- hard exudates and other 'background' changes on macula
- check visual acuity
- more common in Type II DM

## Management

### All patients

- optimise glycemic control, blood pressure and hyperlipidemia
- regular review by ophthalmology

### Maculopathy

- if there is a change in visual acuity then intravitreal vascular endothelial growth factor (VEGF) inhibitors

### Non-proliferative retinopathy

- regular observation
- if severe/very severe consider panretinal laser photocoagulation

### Proliferative retinopathy

- panretinal laser photocoagulation
- intravitreal VEGF inhibitors
  - often now used in combination with panretinal laser photocoagulation
  - examples include ranibizumab
  - strong evidence base suggests they both slow progression of proliferative diabetic retinopathy and improve visual acuity
- if severe or vitreous haemorrhage: vitreoretinal surgery

# Hypertensive retinopathy

The table below shows the Keith-Wagener classification of hypertensive retinopathy

| Stage | Features |
|---|---|
| I | Arteriolar narrowing and tortuosity<br>Increased light reflex - silver wiring |
| II | Arteriovenous nipping |
| III | Cotton-wool exudates<br>Flame and blot haemorrhages<br>• These may collect around the fovea resulting in a 'macular star' |
| IV | Papilloedema |

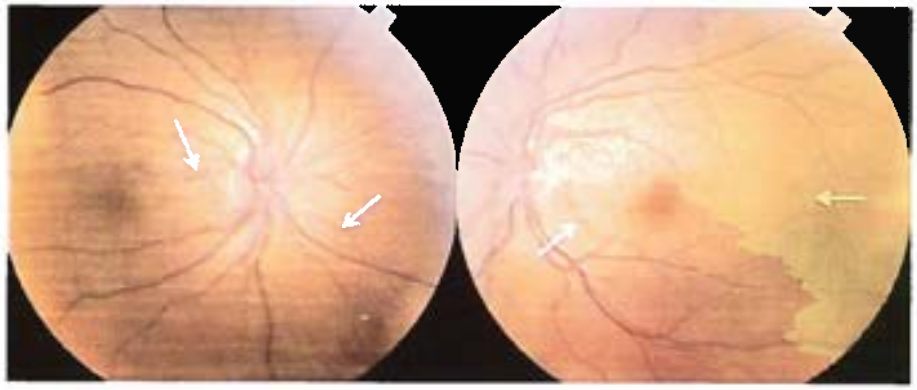
# Angioid retinal streaks

- Angioid retinal streaks are seen on fundoscopy as irregular dark red streaks radiating from the optic nerve head.
- They are caused by degeneration, calcification and breaks in Bruch's membrane.

## Causes

A useful mnemonic for angioid retinal streak is **SLAPPERS**:

- **S** - **Sickle-cell anaemia**
- **L** - Lead poisoning
- **A** - Abetalipoproteinaemia/acromegaly
- **P** - **Paget's disease** /phacomatoses (tuberous, sclerosis, neurofibromatosis, Sturge-Weber)
- **P** - **Pseudoxanthoma elasticum**
- **E** - Ehlers-Danlos syndrome
- **R** - Raised calcium or phosphate
- **S** - Short people (dwarfism).



## Central retinal artery occlusion

- causes sudden unilateral visual loss
- due to thromboembolism (from atherosclerosis) or arteritis (e.g. temporal arteritis)
- features include afferent pupillary defect, 'cherry red' spot on a pale retina

## Central retinal vein occlusion

Central retinal vein occlusion (CRVO) is a differential for sudden painless loss of vision.

### Risk factors

- increasing age
- hypertension
- cardiovascular disease
- glaucoma
- polycythaemia

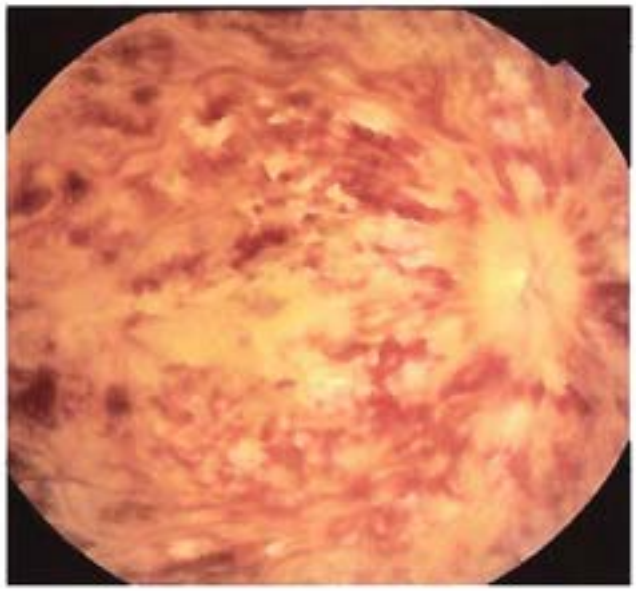
### Features

- sudden, painless reduction or loss of visual acuity, usually unilaterally
- fundoscopy
    - widespread hyperaemia
    - severe retinal haemorrhages - 'stormy sunset'

A key differential is branch retinal vein occlusion (BRVO) - this occurs when a vein in the distal retinal venous system is occluded and is thought to occur due to blockage of retinal veins at arteriovenous crossings. It results in a more limited area of the fundus being affected.

### Management

- the majority of patients are managed conservatively
- indications for treatment in patients with CRVO include:
    - macular oedema - intravitreal anti-vascular endothelial growth factor (VEGF) agents
    - retinal neovascularization - laser photocoagulation



Fundoscopy image showing a central retinal vein occlusion

**Differentiating posterior vitreous detachment, retinal detachment and vitreous haemorrhage**

| Posterior vitreous detachment | Retinal detachment | Vitreous haemorrhage |
|---|---|---|
| Flashes of light (photopsia) - in the peripheral field of vision<br>Floaters, often on the temporal side of the central vision | Dense shadow that starts peripherally progresses towards the central vision<br>A veil or curtain over the field of vision<br>Straight lines appear curved<br>Central visual loss | Large bleeds cause sudden visual loss<br>Moderate bleeds may be described as numerous dark spots<br>Small bleeds may cause floaters |

## Retinitis

CMV Retinitis: causes hemorrhage at the edge of the area of retinal necrosis

- **Retinitis** is inflammation of the retina in the eye, which may lead to blindness.
- may be caused by several infectious agents, toxoplasmosis, cytomegalovirus and candida.
- Cytomegalovirus retinitis is the most common cause of vision loss in AIDS patients.

# Retinitis pigmentosa

Retinitis pigmentosa primarily affects the peripheral retina resulting in tunnel vision

## Features

- **night blindness is often the initial sign**
- tunnel vision due to loss of the peripheral retina (occasionally referred to as funnel vision)
- fundoscopy: black bone spicule-shaped pigmentation in the peripheral retina, mottling of the retinal pigment epithelium

## Associated diseases

- Refsum disease: cerebellar ataxia, peripheral neuropathy, deafness, ichthyosis
- Usher syndrome
- abetalipoproteinemia
- Lawrence-Moon-Biedl syndrome
- Kearns-Sayre syndrome
- Alport's syndrome

Fundus showing changes secondary to retinitis pigmentosa

# Age related macular degeneration

Age-related macular degeneration is the most common cause of blindness in the UK.
Degeneration of the central retina (macula) is the key feature with changes usually bilateral.
ARMD is characterised by degeneration of retinal photoreceptors that results in the formation of drusen which can be seen on fundoscopy and retinal photography.
It is more common with advancing age and is more common in females.

## Risk factors

- **advancing age itself is the greatest risk factor for ARMD**
  - the risk of ARMD increases 3 fold for patients aged older than 75 years, versus those aged 65-74.
- **smoking**
  - current smokers are twice as likely as non-smokers to have ARMD related visual loss, and ex-smokers have a slightly increased risk of developing the condition, (OR 1.13).
- **family history** is also a strong risk factor for developing ARMD
  - first degree relatives of a sufferer of ARMD are thought to be four times more likely to inherit the condition.
- other risk factors for developing the condition include those associated with increased risk of ischaemic cardiovascular disease, such as hypertension, dyslipidaemia and diabetes mellitus.

## Classification

**Traditionally two forms of macular degeneration are seen:**

**dry macular degeneration**

- 90% of cases
- also known as atrophic
- characterised by **drusen** - yellow round spots in Bruch's membrane

**wet macular degeneration**

- 10% of cases
- also know as exudative or neovascular macular degeneration
- characterised by choroidal neovascularisation
- leakage of serous fluid and blood can subsequently result in a rapid loss of vision
- carries worst prognosis

**Recently there has been a move to a more updated classification:**

- early age-related macular degeneration (non-exudative, age-related maculopathy): drusen and alterations to the retinal pigment epithelium (RPE)
- late age-related macular degeneration (neovascularisation, exudative)

## Clinical features

Patients typically present with a subacute onset of visual loss with:

- a reduction in visual acuity, particularly for near field objects
- difficulties in dark adaptation with an overall deterioration in vision at night
- fluctuations in visual disturbance which may vary significantly from day to day
- they may also suffer from photopsia, (a perception of flickering or flashing lights), and glare around objects

## Signs:

- distortion of line perception may be noted on Amsler grid testing
- fundoscopy reveals the presence of drusen, yellow areas of pigment deposition in the macular area, which may become confluent in late disease to form a macular scar.
- in wet ARMD well demarcated red patches may be seen which represent intra-retinal or sub-retinal fluid leakage or haemorrhage.

## Investigations:

- slit-lamp microscopy is the initial investigation of choice, to identify any pigmentary, exudative or haemorrhagic changes affecting the retina which may identify the presence of ARMD. This is usually accompanied by colour fundus photography to provide a baseline against which changes can be identified over time.
- fluorescein angiography is utilised if neovascular ARMD is suspected, as this can guide intervention with anti-VEGF therapy. This may be complemented with indocyanine green angiography to visualise any changes in the choroidal circulation.
- ocular coherence tomography is used to visualise the retina in three dimensions, because it can reveal areas of disease which aren't visible using microscopy alone.

## Managment

### Treatment

- the AREDS trial examined the treatment of dry ARMD in 3640 subjects. It showed that a combination of zinc with anti-oxidant vitamins A,C and E reduced progression of the disease by around one third. Patients with more extensive drusen seemed to benefit most

from the intervention. Treatment is therefore recommended in patients with at least moderate category dry ARMD.

- **vascular endothelial growth factor (VEGF)**
  - VEGR is a potent mitogen and drives increased vascular permeability in patients with wet ARMD
  - a number of trials have shown that use of anti-VEGF agents can limit progression of wet ARMD and stabilise or reverse visual loss
  - evidence suggests that they should be instituted within the first two months of diagnosis of wet ARMD if possible
  - examples of anti-VEGF agents include ranibizumab, **bevacizumab and pegaptanib, the agents are usually administered by 4 weekly injections.**
- laser photocoagulation does slow progression of ARMD where there is new vessel formation, although there is a risk of acute visual loss after treatment, which may be increased in patients with sub-foveal ARMD. For this reason, anti-VEGF therapies are usually preferred.

## Posterior vitreous detachment

- **Posterior vitreous detachment is the separation of the vitreous membrane from the retina.**
- This occurs due to natural changes to the vitreous fluid of the eye with ageing.
- Posterior vitreous detachment is a common condition that does not cause any pain or loss of vision.
- However, rarely the separation of the vitreous membrane can lead to tears and detachment of the retina.
- It is important to rule out retinal tears or retinal detachment in anyone with suspected posterior vitreous detachment, as they may result in permanent loss of vision.

### Epidemiology:

- Occur in over 75% of people over the age of 65
- More common in females

### Risk factors:

- As people age, the vitreous fluid in the eye becomes less viscous, and thus, does not hold its shape as well. Therefore, it pulls the vitreous membrane away from the retina towards the centre of the eye.
- Highly myopic (near-sighted) patients are also at increased risk of developing posterior vitreous detachment earlier in life. This is because the myopic eye has a longer axial length than an emmetropic eye.

### Symptoms:

- **The sudden appearance of floaters** (occasionally a ring of floaters temporal to central vision)
- **Flashes of light in vision**
- Blurred vision
- Cobweb across vision
- The appearance of a dark curtain descending down vision (means that there is also retinal detachment)

### Signs:

- Weiss ring on ophthalmoscopy (the detachment of the vitreous membrane around the optic nerve to form a ring-shaped floater).

### Investigations:

- All patients with suspected vitreous detachment should be examined by an ophthalmologist within 24hours to rule out retinal tears or detachment.

### Management:

- Posterior vitreous detachment alone does not cause any permanent loss of vision. Symptoms gradually improve over a period of around 6 months and therefore no treatment is necessary.
- If there is an associated retinal tear or detachment the patient will require surgery to fix this.

## Papilledema

Papilledema describes optic disc swelling that is caused by increased intracranial pressure. It is almost always bilateral.

The following features may be observed during fundoscopy:

- venous engorgement: usually the first sign
- loss of venous pulsation: although many normal patients do not have normal pulsation
- blurring of the optic disc margin
- elevation of optic disc
- loss of the optic cup
- Paton's lines: concentric/radial retinal lines cascading from the optic disc

### Causes of papilledema

- space-occupying lesion: neoplastic, vascular
- malignant hypertension

- idiopathic intracranial hypertension
- hydrocephalus
- hypercapnia

**Rare causes include**

- hypoparathyroidism and hypocalcaemia
- vitamin A toxicity

## Optic neuritis

### Causes

- multiple sclerosis: the commonest associated disease
- diabetes
- syphilis

### Features

- unilateral decrease in visual acuity over hours or days
  - Visual loss typically occurs over days rather than hours. Sudden visual loss due to optic neuritis is very unusual.
  - Optic neuritis presents with a particular type of central visual loss - a central scotoma.
- poor discrimination of colours, 'red desaturation'
- The retrobulbar neuritis seen with ethambutol may be unilateral or bilateral; as such unilateral symptoms do not preclude the diagnosis.
- pain worse on eye movement
- relative afferent pupillary defect
- central scotoma
- Most cases of optic neuritis are retrobulbar and hence there are no abnormalities on fundoscopy.
  - the most likely finding on fundoscopy ☐ Normal optic disc

### Diagnosis

- MRI with gadolinium of the brain **will likely show >>** enhancement of the optic nerve
- Abnormal visual evoked potentials (VEP)

### Management

- high-dose steroids
- recovery usually takes 4-6 weeks

### Prognosis

- MRI: if > 3 white-matter lesions, 5-year risk of developing multiple sclerosis is c. 50%

## Sudden loss of vision

Sudden loss is a frightening symptom for patients. It may represent an ongoing issue or only be temporary.
The term transient monocular visual loss (TMVL) describes a sudden, transient loss of vision that lasts less than 24 hours.

**The most common causes** of a sudden painless loss of vision are as follows:

- ischemic/vascular (e.g. thrombosis, embolism, temporal arteritis etc.). This includes recognized syndromes e.g., occlusion of central retinal vein and occlusion of central retinal artery
- vitreous hemorrhage
- retinal detachment
- retinal migraine

### Ischemic/vascular

- often referred to as 'amaurosis fugax'
- wide differential including large artery disease (atherothrombosis, embolus, dissection), small artery occlusive disease (anterior ischemic optic neuropathy, vasculitis e.g., temporal arteritis), venous disease and hypoperfusion
- may represent a form of **transient ischaemic attack** (TIA). It should therefore be treated in a similar fashion, with aspirin 300mg being given
- altitudinal field defects are often seen: 'curtain coming down'
- ischemic optic neuropathy is due to occlusion of the short posterior ciliary arteries, causing damage to the optic nerve

### Vitreous hemorrhage

- causes: **diabetes**, bleeding disorders, anticoagulants
- features may include sudden visual loss, dark spots

### Retinal detachment

- features of vitreous detachment, which may precede retinal detachment, include flashes of light or floaters (see below)

## Third nerve palsy

### Features:

- **Eye is deviated 'down and out'** (divergent squint).
- **Ptosis.**
- **Mydriasis** (Pupil may be dilated) (sometimes called a 'surgical' third nerve palsy).
- **Unreactive** pupil to **light.**
- **Pain if** due to a posterior communicating artery aneurysm.

Ptosis + **Miosis** (Constricted pupil) >>> **Horner's** Syndrome
Ptosis + **Mydriasis** (Dilated pupil) >>> **3 rd. Nerve palsy**

### Causes:

- DM
- Vasculitis e.g. temporal arteritis, SLE
- False localizing sign due to uncal herniation through tentorium if raised ICP
- **Posterior communicating artery aneurysm** (pupil dilated)
- Cavernous sinus thrombosis
- **Weber's syndrome**: Ipsilateral third nerve palsy with contralateral hemiplegia -caused by midbrain strokes (cerebral peduncle).
- Other possible causes: amyloid, multiple sclerosis

*This term is usually associated with sixth nerve palsies but it may be used for a variety of neurological presentations.

**Painful third nerve palsy = posterior communicating artery aneurysm** (i.e., EX. **Third nerve palsy** with **headache** and meningism >>> should exclude posterior communicating artery aneurysm).

## Holmes-Adie pupil

Holmes-Adie pupil is a benign condition most commonly seen in women. It is one of the differentials of a dilated pupil.

### Overview

- unilateral in 80% of cases
- dilated pupil
- once the pupil has constricted it remains small for an abnormally long time
- slowly reactive to accommodation but very poorly (if at all) to light

### pathophysiology

- Viral or bacterial infection causes □ damage to neurons in the ciliary ganglion, located in the posterior orbit, that provides parasympathetic control of eye constriction.
- damage to the dorsal root ganglia of the spinal cord □ problems with autonomic control of the body.

**Diagnosis:** testing with low dose (1/8%) pilocarpine may constrict the tonic pupil due to cholinergic denervation super-sensitivity. A normal pupil will not constrict with the dilute dose of pilocarpine.

**Holmes-Adie syndrome:** association of Holmes-Adie pupil with absent ankle/knee reflexes

## Argyll-Robertson pupil

Argyll-Robertson pupil is one of the classic pupillary syndrome.
It is sometimes seen in neurosyphilis.
A mnemonic used for the Argyll-Robertson Pupil (ARP) is Accommodation Reflex Present (ARP) but Pupillary Reflex Absent (PRA)

### Features

- small, irregular pupils
- no response to light but there is a response to accommodate

### Causes

- diabetes mellitus
- syphilis

## Horner's syndrome

### Features

- miosis (small pupil)
- enophthalmos* (sunken eye)
- ptosis
- **anhidrosis (loss of sweating one side)**

### Distinguishing between causes

- heterochromia (difference in iris colour) is seen in congenital Horner's
- anhidrosis: see below
- pharmacologic tests
  - can be useful to confirm the diagnosis of Horner syndrome and **localize** the lesion
  - apraclonidine drops (an alpha-adrenergic agonist) can be used: causes pupillary dilation in Horner's syndrome due to denervation **supersensitivity** but produces mild pupillary constriction in the normal pupil by down-regulating the norepinephrine release at the synaptic cleft

| Central lesions | Pre-ganglionic lesions | Post-ganglionic lesions |
|---|---|---|
| Anhidrosis of the face, arm and trunk | Anhidrosis of the face | No anhidrosis |
| Stroke<br>Syringomyelia<br>Multiple sclerosis<br>Tumour<br>Encephalitis | Pancoast's trumour<br>Thyroidectomy<br>Trauma<br>Cervical rib | Carotid artery dissection<br>Carotid aneurysm<br>Cavernous sinus thrombosis<br>Cluster headache |

*In reality the appearance is due to a narrow palpebral aperture rather than true enophthalmos

## Relative afferent pupillary defect

Also known as the Marcus-Gunn pupil, a relative afferent pupillary defect is found by the 'swinging light test'.
It is caused by a lesion anterior to the optic chiasm i.e. optic nerve or retina

**Finding**: the affected and normal eye appears to dilate when light is shone on the affected

### Causes

- retina: detachment
- optic nerve: optic neuritis e.g. multiple sclerosis

### Pathway of pupillary light reflex

- afferent: retina → optic nerve → lateral geniculate body → midbrain
- efferent: Edinger-Westphal nucleus (midbrain) → oculomotor nerve

### Swinging flashlight test & Relative afferent pupillary defect

RAPD (Marcus Gunn pupil)

- The Marcus Gunn pupil is a relative afferent pupillary defect indicating a decreased pupillary response to light in the affected eye
- In the swinging flashlight test, a light is alternately shone into the left and right eyes.
- A normal response would be equal constriction of both pupils, regardless of which eye the light is directed at. This indicates an intact direct and consensual pupillary light reflex.
- When the test is performed in an eye with an afferent pupillary defect, light directed in the affected eye will cause only mild constriction of both pupils (due to decreased response to light from the afferent defect), while light in the unaffected eye will cause a normal constriction of both pupils (due to an intact efferent path, and an intact consensual pupillary reflex). Thus, light shone in the affected eye will produce less pupillary constriction than light shone in the unaffected eye.
- **A positive RAPD is due to retinal or optic nerve disease.**

**due to the consensual response of the pupillary light reflex, shining light in the unaffected eye will produce bilateral miosis.**

- shining light in the affected eye will not produce miosis because the afferent limb of the pupillary light reflex pathway is damaged (eg: optic neuritis)
- However, **due to the bilateral projections of nerves from the Edinger-Westphal nucleus**, light shined in the **unaffected eye** will produce **bilateral miosis**. This phenomenon is called a **consensual response**.

## Foster- Kennedy's syndrome

It is a combination of **optic atrophy** and **central scotoma**, **contralateral papilloedema and anosmia**.
It is caused by **optic and olfactory nerve compression** and **raised intracranial pressure.**
This is often secondary to a mass such as an olfactory groove meningioma.
Patients may also have other symptoms of raised intracranial pressure such as nausea and vomiting, and frontal symptoms such as emotional lability and memory loss.

## Anisocoria

- is a condition characterized by an unequal size of the eyes' pupils.
- Affecting 20% of the population,
- it can be an entirely harmless condition or a symptom of more serious medical problems
- **The history of anisocoria, with headaches and diplopia should ring alarm bells, in that a life-threatening posterior communicating artery aneurysm/berry aneurysm needs to be excluded urgently.**

## Mydriasis

### Causes of mydriasis (large pupil)

- third nerve palsy
- Holmes-Adie pupil
- traumatic iridoplegia
- phaeochromocytoma
- congenital

### Drug causes of mydriasis

- topical mydriatics: tropicamide, atropine
- sympathomimetic drugs: amphetamines, **cocaine**
- anticholinergic drugs: tricyclic antidepressants

Anisocoria may result in apparent mydriasis, due to the difference with the other pupil.

## Eye signs in Systemic diseases

- **Lisch nodules** of the iris are golden nodules occurring bilaterally in the teenage years onwards in Neurofibromatosis type 1 (NF-1). **Axillary freckles** appear at 10 years of age, while cafe au lait spots increase in size and number throughout childhood.
- **Brushfield spots** of the iris are found in people with Down syndrome.
- **Kayser-Fleischer rings** are due to copper deposition in Descemet's membrane of the cornea.
- **Band keratopathy** is caused by calcium deposition in Bowman's layer of the cornea. Patients who present with band keratopathy should have a serum calcium and phosphate level
- **Ectopia lentis with aortic regurgitation** >> Marfan syndrome (Lens dislocation (classically upwards)).
  Inferior dislocated lens >> consistent with a diagnosis of homocytinstinuria.
- **Roth's spots haemorrhages in the retina >> associated with subacute bacterial endocarditis.** also, seen in leukaemia.
- **'black sunburst'** - a chorioretinal scar, which is one of the commoner retinal manifestations of Sickle cell disease (SCD) and pathognomonic.

## Fundoscopic features

- **Cytomegalovirus *(CMV) retinitis***
  - secondary to human immunodeficiency virus (HIV)
  - Fundoscopy of the left eye revealed an extensive **'brushfire-like' lesion** in the major superior temporal arcade with a large patch of white fluffy lesion mixed with extensive **retinal haemorrhages.**
- **Ocular histoplasmosis and syphilitic choroiditis** would give a fundus picture of **multiple whitish lesions**.
- **Syphilitic neuroretinitis** would normally give a picture of a **macular star exudation**.
- **Tuberculous periphlebitis** gives a picture of **perivenous sheathing and minimal retinal haemorrhages**.

## Rheumatoid arthritis: ocular manifestations

Ocular manifestations of rheumatoid arthritis are common, with 25% of patients having eye problems.

### Ocular manifestations:

- **Keratoconjunctivitis sicca (most common)**, It is **usually bilateral** and associated more with dryness, burning and itch.
- Keratitis
- Corneal ulceration
- **Episcleritis** (erythema)
- **Scleritis** (erythema and **pain**)

The difference between Scleritis and Episcleritis is the presence of **pain.**
**Scleritis is painful**,
Episcleritis is not painful.

### Iatrogenic:

- Steroid-induced cataracts
- Chloroquine retinopathy

## Temporal arteritis

It is large vessel vasculitis which overlaps with polymyalgia rheumatica (PMR).
Histology shows changes which characteristically 'skips' certain sections of affected artery whilst damaging others.

### Features:

- Typically patient > 60 years old
- Usually rapid onset (e.g. < 1 month)
- Headache (found in 85%)
- Jaw claudication (65%)
- Visual disturbances secondary to **anterior ischemic optic neuropathy**
- Tender, palpable temporal artery
- Features of PMR: aching, morning stiffness in proximal limb muscles (not weakness)
- Also lethargy, depression, low-grade fever, anorexia, night sweats

### Investigations:

- Raised inflammatory markers: ESR > 50 mm/hr (note ESR < 30 in 10% of patients). CRP may also be elevated
- Temporal artery biopsy: skip lesions may be present
- Note creatine kinase and EMG normal

### Treatment:

- **High-dose prednisolone** - there should be a **dramatic response**, if not the diagnosis should be reconsidered.
- **Urgent** ophthalmology review. Patients with visual symptoms should be seen the same-day by an ophthalmologist. Visual damage is often irreversible.

**Example:** A 74-year-old man presents with a severe throbbing headache on the right side of his head. He has now had this pain for around 6-7 days but reports no obvious trigger. There have been no visual disturbances or episodes of limb weakness. Neurological examination is unremarkable. The right side of his head is tender to touch but he cannot remember falling. >>> It is **temporal arteritis** >>> the most important initial step is to **give high-dose oral prednisolone** to prevent ocular complications.

## Important collections

### Double Vision

**Monooccular causes:**

- Cataract.
- Corneal disease.
- Lens discoloration.
- Refractory errors.
- Macular disease.

**Binocular:**

**Brain:**

- internuclear ophthalmoplegia: M.S, stroke, tumors, Werneck's encephalopathy
- brain stem lesion.

**Nerve**:3rd,4th,6th

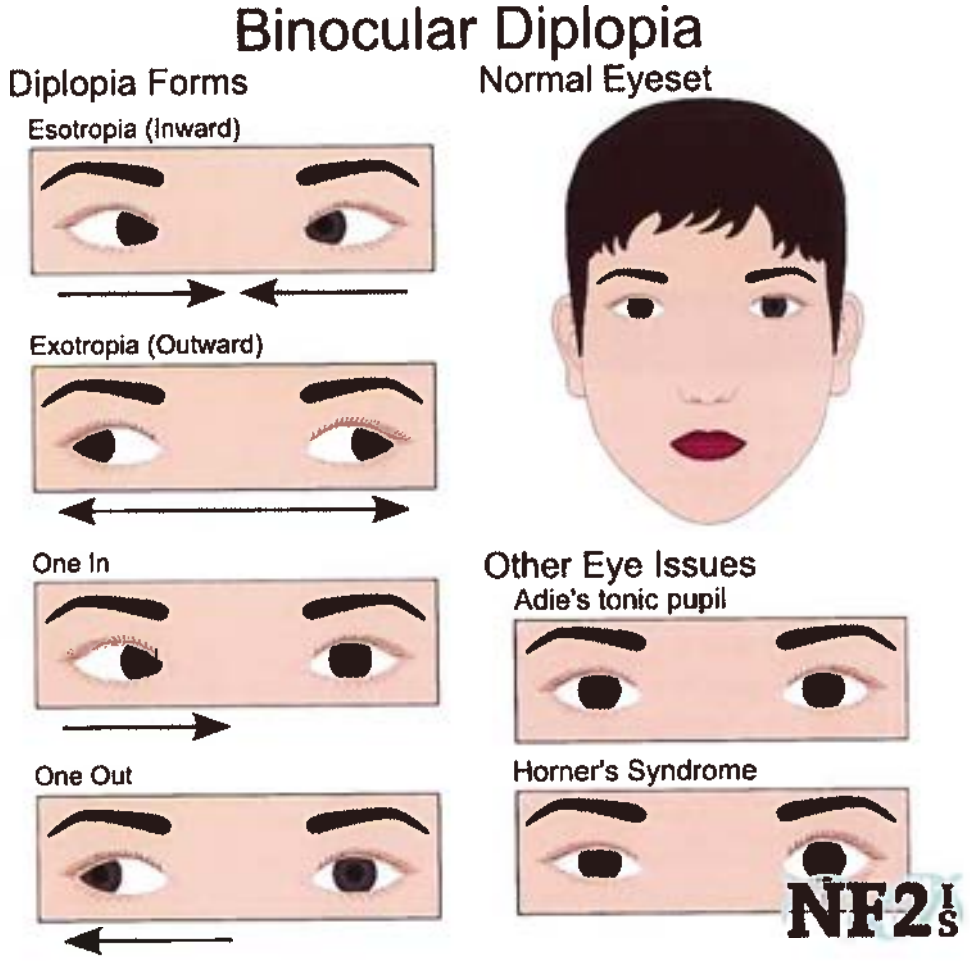
**Neuromuscular**: Myasthenia Gravis and botulism.

**Orbital:** cellulitis, tumor, fracture.

**Muscles:** graves ophthalmopathy, orbital myositis, genetic myopathy, CPEO or KEARN-SAYER.

**Drugs:**
D-penicillamine, Aminoglycosides, phenytoin, anesthesia.

MONOMER =G2M2C2S
Graves disease, GBS, M.gravis : botulism, eaton-lumbert syndrome - Miller-fisher - cranial nerve palsy, Chronic progressive extrinsic ophthalmoplegia (CPEO).
-sinus thrombosis: cavernous sinus with multiple nerve affection unilaterally.



- **Variable diplopia:**

**Remember:**

- **Retina and macula are responsible for:** color and night vision.
- **optic nerve is responsible for:** field and acuity

## Common exam cases

Variable diplopia = Bizzare.

- Myasthenia gravis.
- Gravis disease.
- Cavernous sinus thrombosis.

**Acute orbitopathy:** acute proptosis , ocular injection, diplopia.

- Infection: Herps zoster ophthalmicus, fungal infection(mucormycosis).
- Inflammation: sarcoidosis wegners granulomatosis.
- Vascular: cavernous sinus thrombosis, giant cell arteritis
- Tumors: meningioma, lymphoma, primary orbital tumor.

## Painful opthalmolpegia:

- Vascular: Cavernous Sinus thrombosis, giant cell arteritis , ischemia, 3rd nerve palsy.
- Neoplastic: pit adenoma or apoplexy, orbital tumors, metastatic Nasopharyngeal tumors.
- Infective: sinusitis, herps zoster opthalmicus , mucormycosis , sarcoidosis, orbital pseudo tumors.

## Causes of cavernous sinus syndrome:

- Cavernous sinus thrombosis.
- Extracavernous carotid artery aneurysm.
- Posterior communicating artery aneurysm.
- carotico- cavernous fistula.
- Neoplasms.
- Infections (sinusitis, mucormycosis, Herps zoster opthalmicus).

## Visual disturbance and how to proceed in opth case in paces

visual loss to patient may mean

- Reduced Visual acuity
- Blurred vision
- Abnormal Colored vision

So, start by open statement **(tell me about your symptoms)**

**Then:**

1. **Onset**

**Acute onset:**

**A. Ocular:**

- Retinal detachment .
- CRA/CRV occlusion.
- Acute closed angle glaucoma.
- Ant. Uveitis.
- AION (anterior ischemic optic neuropathy).
- Vitreous hemorrhage.

**Monomer: CRA3V**

**B. Non ocular** = Amaurosis fugax: curtain coming down lasting for minutes/hours.

TIA, Temporal artritis , Hypotension, Hypoglycemia, Migraine and M.S.

**Monomer: T2H2M2**

**Gradual onset:**

**A. a.Non - Ocular:**

**H**TN.
**D**.M
**R**etinitis Pigmentosa.
**A**cromegally.
**T**hyrotoxicosis.

Eye:

- Open angel glucoma.
- Cataract.
- Macular degeneration.

**Monomer: Hdrate**

**B. ocular:**

Papilledema.

Optic n. compression.

M.S: subacute onset of painful visual loss over hrs./days recovery in 2-4 wks.

2. **Unilat. Or bilateral:**
   - Unilateral: ocular / optic n. pathology.
   - Bilateral: lesion behind optic chiasm.
3. **extend of visual loss:**
   - which part affected?
   - all, top half, bottom half, sides, central

**N.B:** Central scotomas: optic neuropathy

Bitemporal hemanopia : patient will complain from colliding into peripheral objects.

Homonymous hemianopia: patient will complain from difficult reading lines across the page.

4. **Progression and recovery**
5. **eye pain**
   - optic neuritis: deep, dull, retroorbital pain more on moving the eye.
   - Angle closure glaucoma.
   - Iritis.
   - thyroid eye disease.
6. **Gritty or burning eye:** cellulitis, conjunctivitis ,thyroid eye, corneal ulceration.
7. **Other symptoms:**
   - Diplopia.
   - Abnormal Color vision
   - Other Symptoms & Signs : flashes, halos, zigzag …etc.
8. **Associated Neurological symptoms:** headache,increased **IC tension.**

**Past medical history:**

- IHD, Dm, HTN, AF
- Vitamin B12.

- M.S.
- folate deficiency.
- Malignancy.
- graves D.
- Marfan Syndrome.

**Family history:**

- Libber's optic atrophy
- Retinitis pigmentosa.

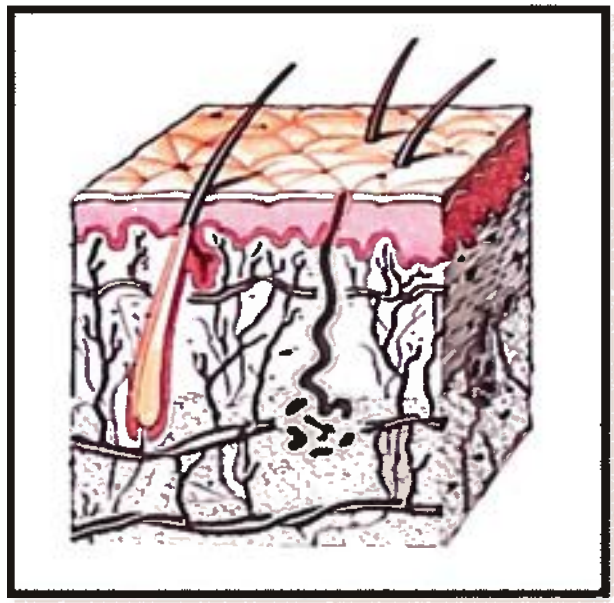
**Medications:**

- optic neuropathy: INH, ethambutol, CSA, cisplatin, Vincristine, phenytoin, carbamazepine.

**Social history:**

Smoking, diet, lead, Carbon monoxide.

# Dermatology



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| Medication | Mode of action | Notes |
|---|---|---|
| Prostaglandin analogues (e.g. latanoprost) | Increases uveoscleral outflow | Once daily administration<br><br>Preferred first-line therapy. should be used first-line in patients with a history of asthma.<br>**Adverse effects:**<br>• brown pigmentation of the iris,<br>• growth of eyelashes<br>• Epithelial keratopathy<br>• Systemic: paresthesia, hypokalemia, renal stones, acidosis. and aolastic anemia. |
| Beta-blockers (e.g. timolol, betaxolol) | Reduces aqueous production | Should be avoided in asthmatics and patients with heart block |
| Sympathomimetics (e.g. brimonidine, an alpha2-adrenoceptor agonist) | Reduces aqueous production and increases outflow | Avoid if taking MAOI or tricyclic antidepressants<br><br>Adverse effects include hyperaemia |
| Carbonic anhydrase inhibitors (e.g. Dorzolamide) | Reduces aqueous production | Systemic absorption may cause sulphonamide-like reactions |
| Miotics (e.g. pilocarpine, a muscarinic receptor agonist) | Increases uveoscleral outflow | Adverse effects included a constricted pupil, headache and blurred vision |

Surgery in the form of a trabeculectomy may be considered in refractory cases.

## Tunnel vision

Tunnel vision is the concentric diminution of the visual fields

### Causes

- papilloedema
- glaucoma
- retinitis pigmentosa
- choroidoretinitis
- optic atrophy secondary to tabes dorsalis
- hysteria

4. Additional features - Cup notching (usually inferior where vessels enter disc), Disc haemorrhages

## Diagnosis:

- Case finding and provisional diagnosis is done by an optometrist
- Referral to the ophthalmologist is done via the GP
- Final diagnosis is done by investigations as below

## Investigations:

- automated perimetry to assess visual field
- slit lamp examination with pupil dilatation to assess optic nerve and fundus for a baseline
- applanation tonometry to measure IOP
- central corneal thickness measurement
- gonioscopy to assess peripheral anterior chamber configuration and depth
- Assess risk of future visual impairment, using risk factors such as IOP, central corneal thickness (CCT), family history, life expectancy

## Management

The majority of patients with primary open-angle glaucoma are managed with eye drops. These aim to lower intra-ocular pressure which in turn has been shown to prevent progressive loss of visual field.

## NICE guidelines:

- first line: prostaglandin analogue (PGA) eyedrop
- second line: beta-blocker, **carbonic anhydrase inhibitor**, or sympathomimetic eyedrop
- if more advanced: surgery or laser treatment can be tried[2]

## Reassessment

- important to exclude progression and visual field loss
- needs to be done more frequently if: IOP uncontrolled, the patient is high risk, or there is progression

# Primary open-angle glaucoma

## presentation and diagnosis

Glaucomas are optic neuropathies associated with raised intraocular pressure (IOP). They can be classified based on whether the peripheral iris is covering the trabecular meshwork, which is important in the drainage of aqueous humour from the anterior chamber of the eye.

In primary open-angle glaucoma (POAG), the iris is clear of the meshwork. The trabecular network functionally offers an increased resistance to aqueous outflow, causing increased IOP.

It is now recognised that a minority of patients with raised IOP do not have glaucoma and vice versa.

## Risk factors:

- increasing age
  - affects < 1'5 in individuals under 55 years of age
  - but up to 10% over the age of 80 years
- genetics
  - first degree relatives of an open-angle glaucoma patient have a 16% chance of developing the disease
- Afro Caribbean ethnicity
- myopia
- hypertension
- diabetes mellitus
- corticosteroids

POAG may present insidiously and for this reason is often detected during routine optometry appointments.

## Features may include

- **peripheral visual field loss - nasal scotomas progressing to 'tunnel vision'**
- decreased visual acuity
- optic disc cupping

## Fundoscopy signs of POAG

1. Optic disc cupping - cup-to-disc ratio >0.7 (normal = 0.4-0.7), occurs as loss of disc substance makes optic cup widen and deepen
2. Optic disc pallor - indicating optic atrophy
3. Bayonetting of vessels - vessels have breaks as they disappear into the deep cup and re-appear at the base

## Diagnosis

- Tonometry: >> Elevated IOP (> 21 mm Hg)
- Gonioscopy: the gold-standard diagnostic test >> Narrowing/closure of the iridocorneal angle.

## Features

- severe pain: may be ocular or headache
- decreased visual acuity
- symptoms worse with mydriasis (e.g. watching TV in a dark room)
- hard, red-eye
- haloes around lights
- semi-dilated non-reacting pupil
- corneal oedema results in dull or hazy cornea
- systemic upset may be seen, such as nausea and vomiting and even abdominal pain

## Management

The management of AACG is an emergency and should prompt urgent referral to an ophthalmologist.

Emergency medical treatment is required to lower the IOP with more definitive surgical treatment given once the acute attack has settled.

**There are no guidelines for the initial medical treatment emergency treatment. An example regime would be:**

- combination of eye drops, for example:
  - a direct parasympathomimetic (e.g. pilocarpine, causes contraction of the ciliary muscle → opening the trabecular meshwork → increased outflow of the aqueous humour)
  - a beta-blocker (e.g. timolol, decreases aqueous humour production)
  - an alpha-2 agonist (e.g. apraclonidine, dual mechanism, decreasing aqueous humour production and increasing uveoscleral outflow)
- intravenous acetazolamide
  - reduces aqueous secretions

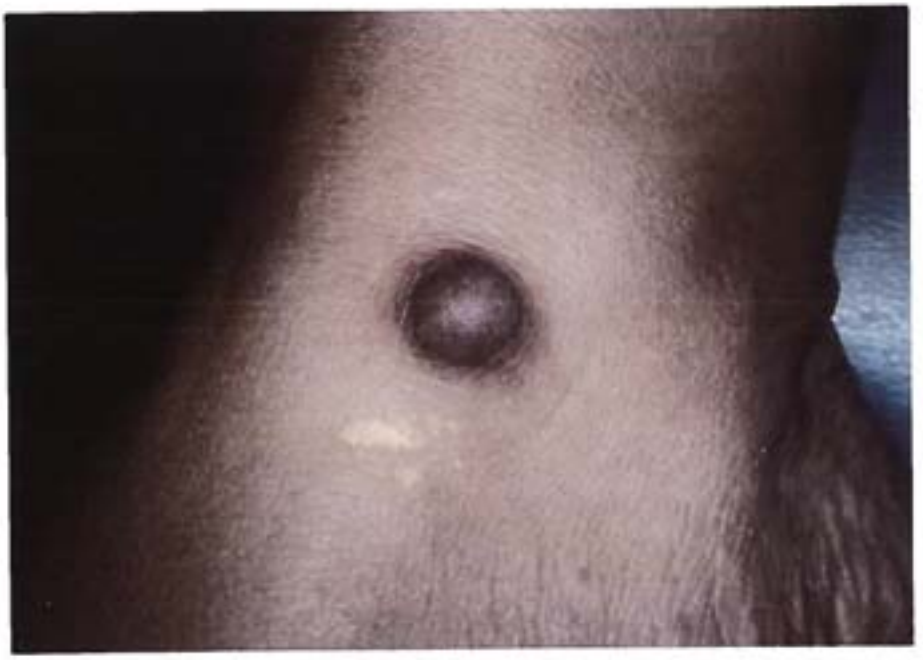
## Definitive management

- laser peripheral iridotomy
  - creates a tiny hole in the peripheral iris → aqueous humour flowing to the angle
  - Anti-VGF

**Atrophy** of the skin may be due to loss of epidermis, dermis or subcutaneous tissue. Thinning of the epidermis presents as skin that appears thin and translucent. Thinning of the dermis and subcutaneous tissue leads to a depression in the skin.

Patch—speckled nevus.

Wheal—the wheals of urticaria.



Nodule—large pigmented dermatofibroma.

# skin diseases alphabetical

## Acanthosis nigricans

Describes **symmetrical**, **brown**, **velvety plaques** that are often found on the **neck**, **axilla** and **groin**.

### Causes:

- **Gastrointestinal cancer**
- **DM**
- Obesity
- Polycystic ovarian syndrome
- Acromegaly
- Cushing's disease
- **Hypothyroidism**
- Familial
- Prader-Willi syndrome
- Drugs: oral contraceptive pill, nicotinic acid

### Management

- first line is **treatment of the underlying cause.**
- In persistent acanthosis nigricans despite treatment of the underlying cause, topical **retinoids** can be tried.

# Acne rosacea

Acne rosacea is a **chronic skin disease** of **unknown** aetiology.

## Features:

- Typically affects **nose**, **cheeks** and **forehead**
- **Flushing** is often first symptom
- **Telangiectasia** are common
- Later develops into **persistent erythema** with **papules** and **pustules**
- **Rhinophyma**
- Ocular involvement: blepharitis
- sunlight may exacerbate symptoms.

## Management:

- Topical metronidazole may be used for mild symptoms (i.e. Limited number of papules and pustules, no plaques).
- More severe disease >> systemic antibiotics: oral Oxytetracycline.
- Recommend daily application of a high-factor **sunscreen.**
- **Camouflage creams** may help conceal redness.
- **Laser** therapy may be for patients with prominent telangiectasia.
- patients with a rhinophyma should be referred to dermatology

Long-term use of **minocycline** ⊗ in particular has been associated with **non-dose dependent blue-grey pigmentation** of skin in the lower legs, and mucosal pigmentation.
Oxytetetracycline and doxycycline can lead to photosensitivity, but skin pigmentation seems to be specific to minocycline rather than a class effect of the tetracyclines.

# Acne vulgaris

Acne vulgaris is a common skin disorder which usually occurs in **adolescence**. It typically affects the face, neck and upper trunk and is characterised by the **obstruction of the pilosebaceous follicle** with keratin plugs which results in **comedones** and **pustules**.

## Epidemiology:

- Affects around **80-90% of teenagers**, 60% of whom seek medical advice.
- Acne may also persist beyond adolescence, **Acne is actually more common in females after the age of 25 years,** with **10-15% of females** and 5% of males over 25 years old being affected.

## Pathophysiology is multifactorial:

- **Follicular epidermal hyperproliferation** resulting in the formation of a keratin plug. This in turn causes obstruction of the pilosebaceous follicle. Activity of sebaceous glands may be controlled by androgen, although levels are often normal in patients with acne.
- Colonisation by the **anaerobic** bacterium **Propionibacterium acnes.**
- Inflammation.

## Acne may be classified into mild, moderate or severe:

- Mild: open and closed comedones with or without sparse inflammatory lesions.
- Moderate acne: widespread non-inflammatory lesions and numerous papules and pustules.
- Severe acne: extensive inflammatory lesions, which may include nodules, pitting, and scarring.

## Management

### A simple step-up management scheme often used in the treatment of acne is as follows:

- Washing the face using a mild soap with lukewarm water twice a day.
- Single topical therapy (**topical Retinoids** and **benzyl peroxide**).
- Combination topical therapy (as above+ **Topical antibiotic)**.
- oral antibiotics:
  - tetracyclines: lymecycline, oxytetracycline, doxycycline
  - tetracyclines should be avoided in pregnant or breastfeeding women and in children younger than 12 years of age
  - erythromycin may be used in pregnancy
  - minocycline is now considered less appropriate due to the possibility of irreversible pigmentation

- a single oral antibiotic for acne vulgaris should be used for a maximum of three months
- a topical retinoid (if not contraindicated) or benzoyl peroxide should always be co-prescribed with oral antibiotics to reduce the risk of antibiotic resistance developing. Topical and oral antibiotics should not be used in combination
- Gram-negative folliculitis may occur as a complication of long-term antibiotic use - high-dose oral trimethoprim is effective if this occurs

- **combined oral contraceptives (COCP) are an alternative to oral antibiotics in women**
  - as with antibiotics, they should be used in combination with topical agents
  - Dianette (co-cyrindiol) is sometimes used as it has anti-androgen properties. However, it has an increased risk of venous thromboembolism compared to other COCPs, therefore it should generally be used second-line, only be given for 3 months and women should be appropriately counselled about the risks
- **oral isotretinoin: only under specialist supervision**
  - pregnancy is a contraindication to topical and oral retinoid tre

There is no role for dietary modification in patients with acne.atment

## Actinic keratosis (AK)

Actinic, or solar, keratosis (AK) is a **common premalignant skin lesion** that develops as a consequence of **chronic sun exposure.**

### Features:

- **Small**, **crusty** or **scaly**, lesions.
- May be pink, red, brown or the same colour as the skin.
- Typically on sun-exposed areas e.g. **temples of head.**
- **Multiple** lesions may be present.

### Management options include:

- **Prevention** of further risk: e.g. sun avoidance, sun cream.
- Fluorouracil cream: typically for a **2 to 3 week course**. The skin will become red and inflamed - sometimes **topical hydrocortisone is given following fluorouracil** to help settle the inflammation.
- **Topical diclofenac**: may be used for mild AKs. Moderate efficacy but much fewer side-effects.
- **Topical Imiquimod**: trials have shown good efficacy.
- Cryotherapy.

- **Curettage and cautery.**

**EX**: Old pt. with multiple number of erythematous, rough lesions on the back of her hands >>> **Actinic keratosis (AK) >>> Topical Fluorouracil cream.**

**EX**: A 67-year-old man is diagnosed with actinic keratosis on his right temple and prescribed fluorouracil cream. One week later he presents as the skin where he is applying treatment has become red and sore. On examination there is no sign of weeping or blistering. What is the most appropriate action? >> This is **a normal reaction to treatment**. Fluorouracil should be continued for at least another week before starting topical steroids. So, **Continue fluorouracil cream + review in 1 week, NOT** (Continue fluorouracil cream + prescribe topical hydrocortisone to use concurrently).

## Alopecia

Alopecia may be divided into scarring (destruction of hair follicle) and non-scarring (preservation of hair follicle).

### Scarring alopecia:

- Trauma, burns
- Radiotherapy
- Lichen planus
- Discoid lupus
- Tinea capitis (scarring may develop in untreated tinea capitis if a kerion develops).

### Non-scarring alopecia:

- Male-pattern baldness.
- **Drugs**: cytotoxic drugs, **C**arbimazole, **C**olchicine, **Heparin (Anti-C**oagulant), **oral C**ontraceptive pill.
- Nutritional: iron and zinc deficiency.
- Autoimmune: alopecia areata.
- Telogen effluvium (hair loss following stressful period e.g. surgery).
- Trichotillomania.

## Alopecia areata

- Alopecia areata is a presumed **autoimmune** condition causing **localised**, **well demarcated** patches of hair loss.
- At the edge of the hair loss, there may be small, broken 'exclamation mark' hairs.
- Hair will regrow in 50% of patients by 1 year, and in 80-90% eventually.
- **Watchful waiting** for **spontaneous remission** and **careful explanation** is therefore sufficient in many patients.
- Neither the British Association of Dermatologists nor Clinical Knowledge Summaries recommend screening for autoimmune disease.
- **Other** treatment options include:
  - **Topical** or **intralesional corticosteroids (triamcinolone).**
  - Topical Minoxidil.
  - Phototherapy.
  - Dithranol.
  - Contact immunotherapy.
  - Wigs.

**EX:** Young female with IDDM e' alopecia areata >> **Intra-lesional triamcinolone**

## Angular stomatitis

- Angular stomatitis describes erythema and fissuring of the skin adjacent to the angle of the mouth.
- The most common cause is *Candida* infection,
- also associated with:
  - allergy,
  - seborrhoeic dermatitis,
  - vitamin B deficiencies,
  - iron deficiency.

## Angiosarcoma

- Angiosarcomas are malignant vascular tumours most commonly seen in elderly men.
- most commonly occur on the scalp and forehead.

- present an infiltrative vascular patch or plaque with super-imposed nodules which may bleed with minor trauma.
- poor prognosis.
- Angiosarcomas can also occur in areas of chronic lymphoedema.

## Basal cell carcinoma

Basal cell carcinoma (BCC) is one of the three main types of skin cancer. Lesions are also known as rodent ulcers and are characterised by slow-growth and local invasion.
Metastases are extremely rare. BCC is the most common type of cancer in the Western world.

### Features

- many types of BCC are described. The most common type is nodular BCC, which is described here
- sun-exposed sites, especially the head and neck account for the majority of lesions
- initially a pearly, flesh-coloured papule with telangiectasia
- may later ulcerate leaving a central 'crater'

**Referral**: generally, if a BCC is suspected, a routine referral should be made

### Management options:

- surgical removal
- curettage
- cryotherapy
- topical cream: imiquimod, fluorouracil
- radiotherapy

Basal cell carcinoma

## (BCC) VS (SCC)

| Basal cell carcinoma | Squamous cell carcinoma |
|---|---|
| Most common | 2nd most common |
| Present in upper part of face | Present in lower part of face (appear most often on the lower lip, ear, and nose.) |
| Does not metastasize and kill by local invasion(rodent ulcer) | Can metastasize |
| presents as a **"pearly"** papule or nodule that grows slowly with **shiny** appearance with telangiectasias and an umbilicated center or ulcer | usually hyperkeratotic **scaly** lesion with crusting and ulceration. often well-defined, superficial, discrete, and hard lesions arising from an indurated, rounded, and elevated base |

# Bullous disorders

## Causes of skin bullae:

- Congenital: **epidermolysis bullosa**
- Autoimmune: **bullous Pemphigoid, pemphigus**
- **Insect bite**
- **Trauma/friction**
- Drugs: **barbiturates, furosemide**

# Bullous Pemphigoid

- Bullous Pemphigoid is an **autoimmune** condition causing **sub-epidermal blistering** of the skin.
- This is secondary to the development of **antibodies against hemidesmosomal proteins BP180 and BP230.**
- Bullous Pemphigoid is more common in **elderly** patients.

## Features:

- **Itchy**, **tense blisters** typically around flexures.
- The blisters usually **heal without scarring**
- **Mouth is usually spared**.

In reality around 10-50% of patients have a degree of mucosal involvement. It would however be unusual for an exam question to mention mucosal involvement as it is seen as a classic differentiating feature between Pemphigoid and Pemphigus.

## Investigations

### Skin biopsy:

- **Perilesional skin biopsy for examination by direct immunofluorescence**
- **Immunofluorescence** shows **IgG** and **C3** at the **dermoepidermal** junction.

## Management:

- Referral to dermatologist for biopsy and confirmation of diagnosis.
- **Oral corticosteroids** are the mainstay of treatment.
- Topical steroids, immunosuppressants and antibiotics are also used.

Bullous pemphigoid

## Café-au-lait spots

Hyperpigmented lesions that vary in colour from light brown to dark brown, with borders that may be smooth or irregular.

### Causes:

- **Neurofibromatosis** type I & II
- **Tuberous sclerosis**
- **Fanconi anaemia**
- **McCune-Albright syndrome**

## Cellulitis

Cellulitis is a term used to describe an inflammation of the skin and subcutaneous tissues, typically due to infection by Streptococcus pyogenes or Staphylococcus aureus.

### Features:

- Commonly occurs on the **shins.**
- Erythema, pain, swelling.
- There may be some associated systemic upset such as fever.

### Management:

- The BNF recommends **flucloxacillin** as **first**-line treatment for mild/moderate cellulitis.
- **Clarithromycin** or **clindamycin** is recommended in patients **allergic** to penicillin.

- Many local protocols now suggest the use of **oral clindamycin** in patients who have **failed to respond to flucloxacillin**.
- Severe cellulitis should be treated with **intravenous benzylpenicillin + flucloxacillin**.

## Contact dermatitis

There are two main types of contact dermatitis:

- **Allergic contact dermatitis**: **type IV hypersensitivity reaction**. **Uncommon** - often seen on the **head following hair dyes**. Presents as an acute weeping eczema which predominately affects **the margins of the hairline rather than the hairy scalp itself. Topical** treatment with a **potent steroid** is indicated.
- **Irritant contact dermatitis**: **common** - non-allergic reaction due to weak acids or alkalis (e.g. **detergents**). Often seen on the **hands**. Erythema is typical, crusting and vesicles are rare.

**Nickel dermatitis** is a **common cause allergic contact dermatitis** and is an example of a type **IV** hypersensitivity reaction. It is often caused by **jewellery** such as **watches**. It is diagnosed by a **skin patch test.**

Cement is a frequent cause of contact dermatitis. The alkaline nature of cement may cause an irritant contact dermatitis whilst the dichromates in cement also can cause an allergic contact dermatitis.

# Dermatitis herpetiformis

Dermatitis herpetiformis is an **autoimmune blistering** skin disorder associated with **coeliac** disease. It is caused by **deposition of IgA** in the **dermis**.

## Features:

- **Itchy**, **vesicular** skin lesions on **the extensor surfaces** (e.g. **elbows**, **knees**, **buttocks**).

## Diagnosis:

- **Skin biopsy**: direct **immunofluorescence** shows **deposition of IgA** in a granular pattern in the upper **dermis**.
- **Anti-gliadin antibody**.

## Management:

- **Gluten-free diet**
- **Dapsone**

# Discoid lupus erythematous

Discoid lupus erythematous is a benign disorder generally seen in **younger females**. It very rarely progresses to SLE (in less than 5% of cases).
It is characterised by **follicular keratin plugs** and is thought to be **autoimmune** in aetiology.

## Features:

- **Erythematous**, **raised rash**, sometimes **scaly**
- May be photosensitive
- More common on **face**, neck, ears and **scalp**
- Lesions heal with atrophy, **scarring** (may cause **scarring alopecia**), and pigmentation.

## Management:

- **topical potent steroid cream**
- **Oral antimalarials** may be used **second**-line e.g. **hydroxychloroquine**
- Avoid sun exposure

**Treatment: Discoid lupus erythematous:1) topical steroids→2)oral hydroxychloroquine**

## Eczema: diagnosis

**UK Working Party Diagnostic Criteria** for **Atopic Eczema:-**

An **itchy skin** condition **in the last 12 months Plus** three or more of:

- **Onset below age 2 years** (not used in children under 4 years).
- History of **flexural involvement** or dermatitis on the cheeks and/or extensor areas in children aged 18 months or under.
- **Visible flexural dermatitis**
- History of generally **dry skin.**
- Personal history of **other atopic disease** in children aged under 4 years, history of atopic disease in a first degree relative may be included.

**Cyclosporine** is a well-used drug in the treatment of **atopic dermatitis (AD).**
It is usually at doses of 2-5 mg/kg.
The pathophysiology of AD is complex but the T **lymphocytes** are involved and it is known that there is an increased production of cytokines particularly **IL-4.**
Cyclosporine is a suppressor of T cells and in that respect works very well in atopic dermatitis and psoriasis.
The side effects of hypertension and renal toxicity limit its use.

## Eczema herpeticum

- Eczema herpeticum describes a **severe primary** infection of the **skin** by herpes simplex virus **HSV** 1 or 2.
- It is more commonly seen in children with atopic eczema and often presents as a **rapidly progressing painful rash.**
- On examination, **monomorphic punched-out erosions (circular, depressed, ulcerated lesions) usually 1–3 mm in diameter** are typically seen.
- As it is potentially life-threatening children should **be admitted** for **IV aciclovir.**

**EX**: A 9-year-old child with a history of atopic eczema presents with a sudden worsening of her skin. Her eczema is usually well controlled with emollients but her parents are concerned as the facial eczema has got significantly worse overnight. She now has painful clustered blisters on both cheeks, around her mouth on her neck. Her temperature is 37.9°C. >>> **Eczema herpeticum >>> hospitalization and IV Acyclovir.**

## Eczema: topical steroids

**Use weakest steroid cream which controls patient's symptoms.**

The table below shows topical steroids by potency:

| Mild | Moderate | Potent | Very potent |
|---|---|---|---|
| **Hydrocortisone** 0.5-2.5% | **Betamethasone** valerate 0.025% (**Betnovate** RD®)<br><br>**Clobetasone butyrate** 0.05% (**Eumovate**) | **Fluticasone** propionate 0.05% (**Cutivate®**)<br><br>Betamethasone valerate 0.1% (Betnovate) | **Clobetasol propionate** 0.05% (**Dermovate®**) |

**Topical steroids:**

- Moderate: Clobetasone butyrate 0.05%
- Potent: Betamethasone valerate 0.1%
- Very potent: Clobetasol propionate 0.05%

Finger tip rule: 1 finger tip unit (FTU) = 0.5 g, sufficient to treat a skin area about twice that of the flat of an adult hand.

Topical steroid doses for eczema in adults:

| Area of skin | Fingertip units per dose |
|---|---|
| Hand and fingers (front and back) | 1.0 |
| A foot (all over) | 2.0 |
| Front of chest and abdomen | 7.0 |
| Back and buttocks | 7.0 |
| Face and neck | 2.5 |
| An entire arm and hand | 4.0 |
| An entire leg and foot | 8.0 |

The BNF makes recommendation on the quantity of topical steroids that should be prescribed for an adult for a single daily application for 2 weeks:

| Area | Amount |
|---|---|
| Face and neck | 15 to 30 g |
| Both hands | 15 to 30 g |
| Scalp | 15 to 30 g |
| Both arms | 30 to 60 g |
| Both legs | 100 g |
| Trunk | 100 g |
| Groin and genitalia | 15 to 30 g |

# Erythema nodosum

## Overview

- inflammation of subcutaneous fat
- typically causes tender, erythematous, nodular lesions
- usually occurs over shins, may also occur elsewhere (e.g. forearms, thighs)
- **usually resolves within 6 weeks**
- **lesions heal without scarring**

## Causes

- infection
  - **streptococci**
  - **tuberculosis**
  - brucellosis
- systemic disease
  - sarcoidosis
  - inflammatory bowel disease
  - Behcet's

- malignancy/lymphoma
- drugs
  - penicillins
  - sulphonamides
  - combined oral contraceptive pill
- **pregnancy**

## Erythema induratum (EI)

- EI is a form of panniculitis characterised by chronic, recurrent, tender, subcutaneous, and sometimes **ulcerated** nodules on the lower legs that may also appear elsewhere.
  - **(Erythema nodosum also commonly associated with TB but do not ulcerate)**
- Females are more frequently affected, with a female: male ratio of 7:1 and it is more frequent in younger females.
- **It is found in association with tuberculosis.**

## Erythrasma

- Erythrasma is a generally **asymptomatic**, **well-demarcated**, flat, slightly scaly, pink or brown **macular rash** usually found in the **groin** or **axillae**.
- It is caused by an overgrowth of the **diphtheroid Corynebacterium minutissimum.**
- Examination with **Wood's light fluorescence** reveals a coral-red fluorescence.
- **Topical miconazole or antibacterial** are usually effective. Oral erythromycin may be used for more extensive infection.

## Erythroderma

Erythroderma is a term used when **more than 95%** of the skin is involved in a **rash** of **any** kind.

### Causes of Erythroderma:

- **Eczema**
- **Psoriasis** (Erythrodermic psoriasis).
- Drugs e.g. **gold**
- **Lymphoma, leukaemia**
- **Idiopathic**

- Erythroderma is an **emergency** as patients are susceptible to **profound dehydration, infection** and **hypothermia**.
- **Methotrexate tab** would be the only correct treatment for someone with erythrodermic psoriasis.
- Steroids could lead to unstable pustular psoriasis and would not generally work.
- Hydroxychloroquine has little effect on psoriasis.
- Topical coal tar and Dithranol are good treatments for chronic plaque psoriasis but are highly irritant and would make the erythroderma much more inflamed and deteriorate his condition.

## Erythema multiforme (EM)

Erythema multiforme is a hypersensitivity reaction that is most commonly triggered by infections. It may be divided into minor and major forms.

### Features:

- Target lesions.
- Initially seen on the **back of the hands / feet** before spreading to the torso.
- **Upper limbs** are more commonly affected than the lower limbs.
- Pruritus is occasionally seen and is usually mild.

If symptoms are severe and involve blistering and mucosal involvement the term **Stevens-Johnson syndrome** is used.

## Causes:

- Viruses: **HSV** (**the most common cause**) about **50% of cases**, Orf (Orf is a skin disease of sheep and goats caused by a parapox virus).
- Idiopathic.
- Bacteria: Mycoplasma, Streptococcus.
- Drugs: **Penicillin V**, **Sulphonamides**, **Carbamazepine**, **Allopurinol**, **NSAIDs**, **Oral contraceptive pill**, Nevirapine.
- Connective tissue disease e.g. SLE.
- **Sarcoidosis.**
- **Malignancy: leukaemia, lymphoma**

# Erysipelas

Erysipelas is a *Streptococcus pyogenes* (a group A streptococcal bacterium) infection of the deep dermis and subcutis.

## Feature

- It is a tender, intensely erythematous, indurated plaque with a sharply demarcated border.
- Its well-defined margin can help differentiate it from other skin infections (eg, cellulitis).

## Treatment

- IV antibiotics such as benzylpenicillin and erythromycin.
- **In a penicillin allergic patient a macrolide is the drug of choice** .There is a 10% cross allergy between cephalosporins and penicillins.

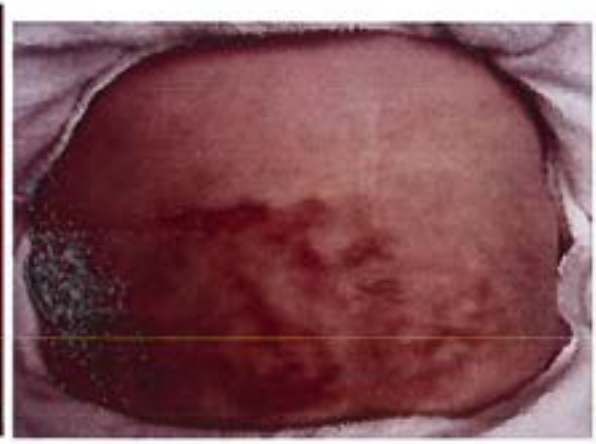
## Complications

- sepsis
- cerebral abscess
- venous sinus thrombosis.

Well-demarcated, erythematous plaque of **erysipelas**.

## Erythema ab igne

- Erythema ab igne is a skin disorder caused by **over exposure** to **infrared radiation.**
- Characteristic features include **reticulated**, **erythematous patches** with **hyperpigmentation** and **telangiectasia**.
- A typical history would be an **elderly women** who **always sits next to an open fire**
- (e.g. **Patient with Hypothyroidism can make patients feel cold and hence more likely to sit next a heater / fire**).
- If the cause is not treated then patients may go on to develop **squamous cell skin cancer.**



## Fungal nail infections (Onychomycosis)

**Onychomycosis** is fungal infection of the nails. This may be caused by:

- **Dermatophytes** - mainly **Trichophyton rubrum**, accounts for **90%** of cases.
- Yeasts - such as Candida.
- Non-Dermatophytes moulds.

### Features:

- **'Unsightly' nails** are **a common reason for presentation.**
- **Thickened**, **rough**, **opaque nails** are the most common **finding**.

### Investigation:

- Nail **clippings**
- **Scrapings** of the affected nail

## Management:

- Treatment is successful in around **50-80%** of people.
- **Diagnosis should be confirmed by microbiology before starting Treatment.**
- **Dermatophytes** infection: **Oral Terbinafine (Lamisil ®)** is currently recommended **first**-line with oral itraconazole as an alternative.
  - **6 weeks - 3 months** therapy is needed for **fingernail** infections.
  - Whilst **toenails** should be treated for **3 - 6 months.**
- Candida infection: mild disease should be treated with topical antifungals (e.g. Amorolfine) whilst more severe infections should be treated with oral itraconazole for a period of 12 weeks.

**EX**: Pt with type **1 DM** presents with **unsightly toenails** affecting the lateral three nails of the left foot. On examination the nails and brown and break easily. **Nail scrapings** demonstrate **Trichophyton rubrum** infection.
>>> **Treatment Oral Terbinafine for 3 – 6 months.**

# Genital warts

- Genital warts (also known as **condylomata accuminata**) are a common cause of attendance at genitourinary clinics.
- They are caused by the many varieties of the human papilloma virus **HPV**, especially types **6** & **11**.
- It is now well established that HPV (primarily types 16,18 & 33) predisposes to cervical cancer.

## Features:

- **Small** (2 - 5 mm) **fleshy protuberances** which are slightly pigmented.
- May bleed or itch

## Management:

- **Topical podophyllum** or **cryotherapy** are commonly used as **first**-line treatments depending on the location and type of lesion.
- Multiple, non-keratinised warts are generally best treated with topical agents whereas solitary, keratinised warts respond better to cryotherapy.
- **Imiquimod** is a topical cream which is generally used **second** line.
- Genital warts are often resistant to treatment and recurrence is common although the majority of anogenital infections with HPV clear without intervention within 1-2 years.

# Herpes simplex virus (HSV)

There are two strains of the herpes simplex virus (HSV) in humans: HSV-1 and HSV-2. Whilst it was previously thought HSV-1 accounted for oral lesions (cold sores) and HSV-2 for genital herpes it is now known there is considerable overlap.

**The most common cause of multiple shallow ulcers in both heterosexual and homosexual males is herpes simplex.**

## Features:

- Primary infection: may present with a **severe gingivostomatitis**
- **Cold sores**
- **Painful genital ulceration**
- **Flu-like symptoms**, **inguinal lymphadenopathy** and **urethral discharge**.

## Diagnosis: **PCR** for **herpes simplex.**

## Management:

- Gingivostomatitis: **oral acyclovir**, chlorhexidine mouthwash.
- Cold sores: topical acyclovir although the evidence base for this is modest.
- Genital herpes: oral acyclovir.
- Some patients with frequent exacerbations may benefit from longer term acyclovir.

## Pregnancy

- elective caesarean section at term is advised if a primary attack of herpes occurs during pregnancy at greater than 28 weeks gestation

**EX**: A 23-year-old man presents with a three day history of general malaise and low-grade temperature. Yesterday he developed extensive painful ulceration of his mouth and gums. On examination his temperature is 37.4°C, pulse 84 / min and there is submandibular lymphadenopathy. What is the most likely diagnosis? >>> Gingivostomatitis, a characteristic feature of primary HSV infection.

# Hirsutism and hypertrichosis

**Hirsutism** is often used to describe **androgen-dependent hair growth** in **women**, with **hypertrichosis** being used for **androgen-independent hair growth.**

**Polycystic ovarian syndrome** is **the most common** causes of **hirsutism.**

## Other causes include:

- **Cushing's syndrome**
- **Congenital adrenal hyperplasia**
- Androgen therapy
- Obesity: due to peripheral conversion oestrogens to androgens
- Adrenal tumour
- Androgen secreting ovarian tumour
- Drugs: **Phenytoin, Minoxidil, Cyclosporine, Diazoxide**

## Assessment of hirsutism:

Ferriman-Gallwey scoring system: 9 body areas are assigned a score of 0 - 4, a score > 15 is considered to indicate moderate or severe hirsutism.

## Management of hirsutism:

- Advise weight loss if overweight.
- Cosmetic techniques such as waxing/bleaching - not available on the NHS.
- Consider using **combined oral contraceptive pills** such as **co-cyprindiol (Dianette)** or ethinylestradiol and drospirenone (Yasmin). Co-cyprindiol should not be used long-term due to the increased risk of venous thromboembolism.
- Facial hirsutism: **topical eflornithine** - contraindicated in pregnancy and breast-feeding.

## Causes of hypertrichosis:

- Drugs: **Phenytoin, Minoxidil, Cyclosporine, Diazoxide**
- **Congenital** hypertrichosis lanuginosa.
- **Congenital** hypertrichosis terminalis.
- **Porphyria cutanea tarda**.
- **Anorexia nervosa**.

# Hypersensitivity

The **Gell and Coombs classification** divides hypersensitivity reactions into 4 types:

## Type I – Anaphylactic:

- Antigen reacts with IgE bound to mast cells.
- EX: Anaphylaxis, atopy (e.g. asthma, eczema and hay fever).

## Type II - Cell bound:

- IgG or IgM binds to antigen on cell surface.
- EX: Autoimmune haemolytic anaemia, **ITP**, Goodpasture's, pernicious anemia, acute hemolytic transfusion reactions, rheumatic fever, bullous Pemphigoid, pemphigus vulgaris.

## Type III - Immune complex:

- Free antigen and antibody (IgG, IgA) combine.
- Serum sickness, SLE, post-streptococcal glomerulonephritis, extrinsic allergic alveolitis (especially acute phase).

## Type IV - Delayed hypersensitivity:

- T cell mediated.
- Tuberculosis, tuberculin skin reaction, graft versus host disease (GVHD), allergic contact dermatitis, **scabies**, extrinsic allergic alveolitis (especially chronic phase), multiple sclerosis, Guillain-Barre syndrome.

In recent times a further category has been added:

## Type V:

- Antibodies that recognise and bind to the cell surface receptors, either stimulating them or blocking ligand binding.
- **Graves'** disease, myasthenia **gravis**.

A 15-year-old girl presents with an urticarial rash, angioedema and wheezing. Her mother states that she has just come from her younger sister's party where she had been helping to blow up balloons. What is the most likely diagnosis? >> This is a typical history of **latex allergy**. **Adrenaline** should be given immediately and usual anaphylaxis management followed.

## Hyperhidrosis

Hyperhidrosis describes the **excessive production of sweat**.

### Management options include:

- **Topical aluminium chloride** preparations are **first**-line. Main side effect is skin irritation.
- Iontophoresis: particularly useful for patients with palmar, plantar and axillary hyperhidrosis.
- Botulinum toxin: currently licensed for axillary symptoms.
- Surgery: e.g. endoscopic transthoracic sympathectomy. Patients should be made aware of the risk of compensatory sweating.

## Impetigo

Impetigo is a superficial bacterial skin infection usually caused by either ***Staphylococcus aureus*** or *Streptococcus pyogenes*.

### Features:

- **'Golden', crusted** skin lesions **typically** found **around the mouth.**
- **Very contagious**.

### Management:

#### Limited, localised disease

- Topical Fusidic acid is first-line.
- **Topical retapamulin (Altabax ®)** is used **second**-line if fusidic acid has been ineffective or is not tolerated.
- **If MRSA** is suspected; as in hospital stay and lack of response to fusidic acid; it is not susceptible to either fusidic acid or retapamulin, so **topical mupirocin (Bactroban®)** should therefore be used in this situation.

### Management

#### Limited, localised disease

- NICE Clinical Knowledge Summaries now recommend **hydrogen peroxide 1% cream** for 'people who are not systemically unwell or at a high risk of complications'
  - the change was announced in **2020** by NICE and Public Health England and seems aimed at cutting antibiotic resistance
  - the evidence base shows it is just as effective at treating non-bullous impetigo as a topical antibiotic

- **topical antibiotic creams:**
  - topical fusidic acid
  - topical mupirocin should be used if fusidic acid resistance is suspected
  - MRSA is not susceptible to either fusidic acid or retapamulin. Topical mupirocin should, therefore, be used in this situation

**Extensive disease:**

- Oral flucloxacillin
- Oral erythromycin if penicillin allergic

**School exclusion**

- children should be excluded from school until the lesions are crusted and healed or 48 hours after commencing antibiotic treatment

## Increased skin fragility

- Increased skin fragility is seen in a number of disorders and is used as a clinical test in bullous disorders (**Nikolsky's sign**).
- Other causes include:
  - pemphigus vulgaris
  - porphyria cutanea tarda
  - drug reactions (especially pseudoporphyria).
- Other causes of increased skin fragility (not associated with bullae) include:
  - long term corticosteroid therapy,
  - Ehlers-Danlos syndrome
  - curvy (vitamin C deficiency).

## Isotretinoin

Isotretinoin is an **oral retinoid** used in the treatment of **severe acne**.
Two-thirds of patients have a long term remission or cure following a course of oral Isotretinoin.

### Adverse effects:

- Teratogenicity: **females** should ideally be using **two forms** of contraception (e.g. combined oral contraceptive pill and condoms).
- Dry skin, **eyes** and **lips**: **the most common side-effect of Isotretinoin**.
- Photosensitivity.
- Nose bleeds (caused by dryness of the nasal mucosa).
- Hair thinning.
- Low mood.
- **Raised triglycerides.**
- **Benign intracranial hypertension**: Isotretinoin treatment should not be combined with tetracyclines for this reason.

**Isotretinoin** >>> the most common side-effect **is dry skin**

## Latex allergy

Sensitivity to latex may cause a number of problems:

- Type I hypersensitivity (anaphylaxis)
- Type IV hypersensitivity (allergic contact dermatitis)
- Irritant contact dermatitis

Latex allergy is more common in children with myelomeningocele spina bifida.

**Latex-fruit syndrome**:
It is recognised that many people who are allergic to latex are also allergic to fruits, particularly **banana**, **pineapple**, **avocado**, **chestnut**, **kiwi** fruit, **mango**, passion fruit and **strawberry**.

**EX**: A nurse who is known to have an allergy to latex develops a widespread urticarial rash and facial oedema shortly after eating lunch. Which food is she most likely to have consumed >> **Latex-fruit syndrome**.

## Lentigo maligna

Lentigo maligna is a type of melanoma in-situ.

It typically progresses slowly but may at some stage become invasive causing Lentigo maligna melanoma.

It is flat brown pigmentation with a jagged, irregular edge. The pigmentation on the anterior aspect of the lesion is a darker brown.

## Lichen sclerosus

- Lichen sclerosus was previously termed lichen sclerosus et atrophicus.
- It is an inflammatory condition which usually **affects the genitalia and is more common in elderly females.**
- Lichen sclerosus leads to **atrophy of the epidermis** with **white plaques** forming.

### Features

- white patches that may scar
- itch is prominent
- may result in pain during intercourse or urination

The diagnosis is usually made on clinical grounds but a biopsy may be performed if atypical features are present*

### Management:

- Topical steroids and emollients.
- **Increased risk of vulval cancer.**

**EX:** A 85-year-old lady presents to dermatology clinic complaining of itchy white plaques affecting her vulva. There is no history of vaginal discharge or bleeding. A similar plaque is also seen on her inner thigh. What is the likely diagnosis? >>> **Lichen sclerosus.**

## Lichen simplex chronicus (LSC)

- LSC presents with hyperpigmented, scaly, lichenified plaques.
- Patients may volunteer a history of chronic scratching or manipulation, especially during times of stress.
- The ankles are common sites for LSC.

## Lichen planus

It is a skin disorder of **unknown** aetiology, most probably being immune mediated.

### Features:

- **Itchy**, **papular** rash most common on the **palms**, **soles**, **genitalia** and **flexor surfaces of arms (e.g. flexor aspect of the wrist).**
- Rash often **polygonal** in shape (**violaceous papules**), 'white-lace' pattern on the surface (Wickham's striae).
- **Koebner phenomenon**: (new skin lesions appearing at the site of trauma).
- Oral involvement in around 50% of patients.
- **Nails**: thinning of nail plate, longitudinal ridging.
- It typical affects patients aged **30-60 years**.

Hypertrophy—hypertrophic lichen planus.

**Lichen:**

- **Planus**: purple, pruritic, papular, polygonal rash on flexor surfaces. Wickham's striae over surface. Oral involvement common.
- **Sclerosus:** itchy white spots typically seen on the vulva of elderly women.

## Lichenoid drug eruptions - causes:

- Gold
- Quinine
- Thiazides

## Management:

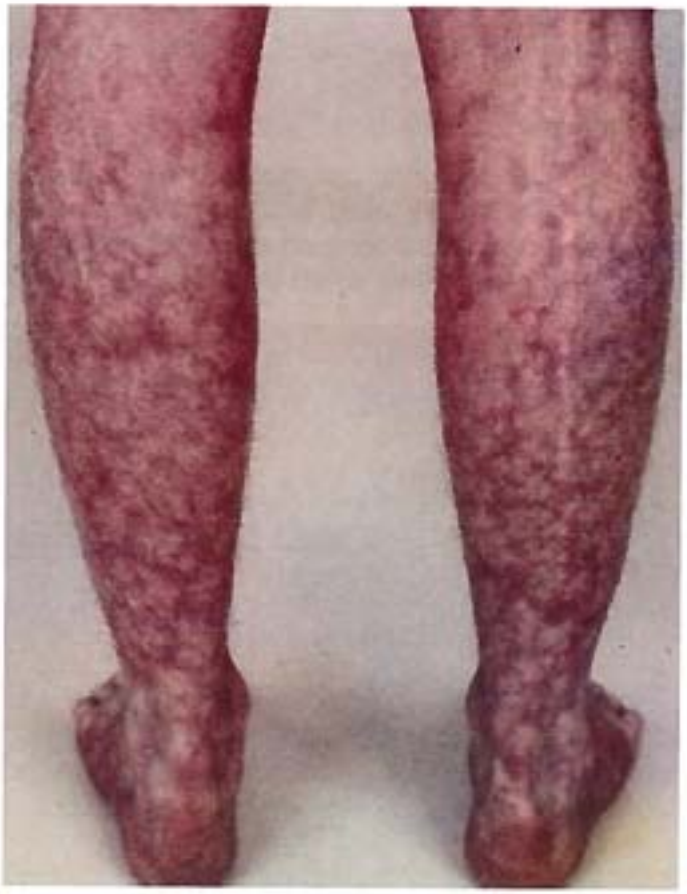
- **Topical steroids** are the mainstay of treatment (e.g. **Clobetasone butyrate "Eumovate cream®").**
- **benzydamine mouthwash or spray is recommended for oral lichen planus**
- Extensive lichen planus may require oral steroids or immunosuppression.

# Livedo reticularis

Livedo reticularis describes an purplish, non-blanching, reticulated rash caused by obstruction of the capillaries resulting in swollen venules.

## Causes

- idiopathic (most common)
- polyarteritis nodosa
- systemic lupus erythematosus
- cryoglobulinaemia
- antiphospholipid syndrome
- Ehlers-Danlos Syndrome
- homocystinuria



# Keloid scars

Keloid scars are **tumour-like lesions** that arise from the connective tissue of a scar and extend beyond the dimensions of the original wound.

## Predisposing factors:

- Ethnicity: more common in people with **dark** skin
- Occur more commonly in **young adults(20-40 years)**, rare in the elderly
- Common sites (in order of decreasing frequency): **sternum**, shoulder, neck, face, extensor surface of limbs, trunk.

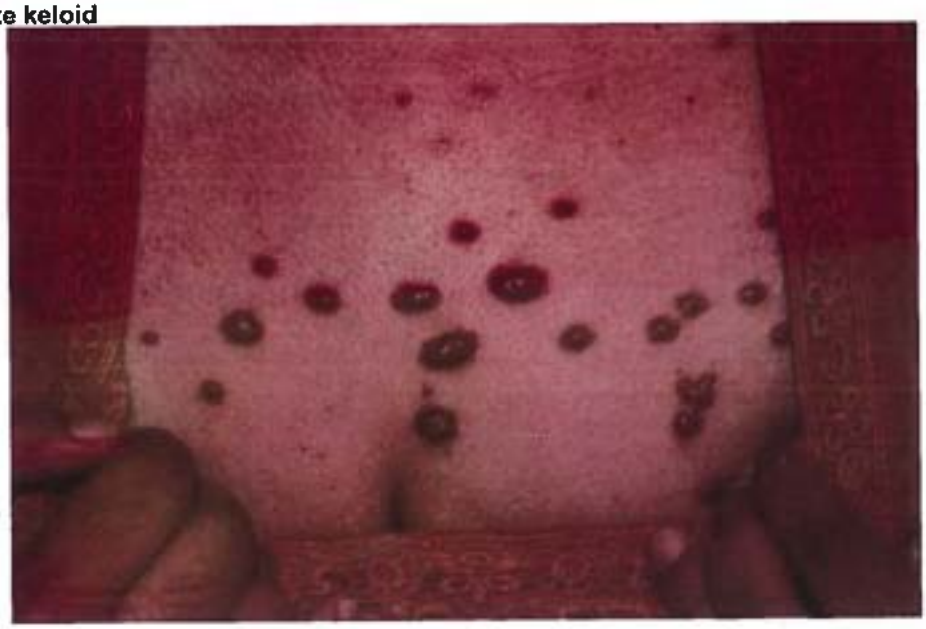
| |
|---|
| Keloid scars - more common in **young**, **black**, **male** adults. |
| Keloid scars are most common on the **sternum.** |

## Treatment:

- **Early** keloids may be treated with **intra-lesional steroids** e.g. **triamcinolone.**
- **Excision** is sometimes required.

Keloid scars are **less** likely if incisions are made along **relaxed** skin tension lines. Langer lines were historically used to determine the optimal incision line. They were based on procedures done on cadavers but have been shown to produce worse cosmetic results than when following skin tension lines

**Guttate keloid**



**Linear kelloid**

## Koebner phenomenon

The Koebner phenomenon describes **skin lesions** which **appear at the site of injury.** It is seen in:

- **Psoriasis**
- **Vitiligo**
- **Warts**
- **Lichen planus**
- **Lichen sclerosus**
- **Molluscum contagiosum**

## Keratoacanthoma

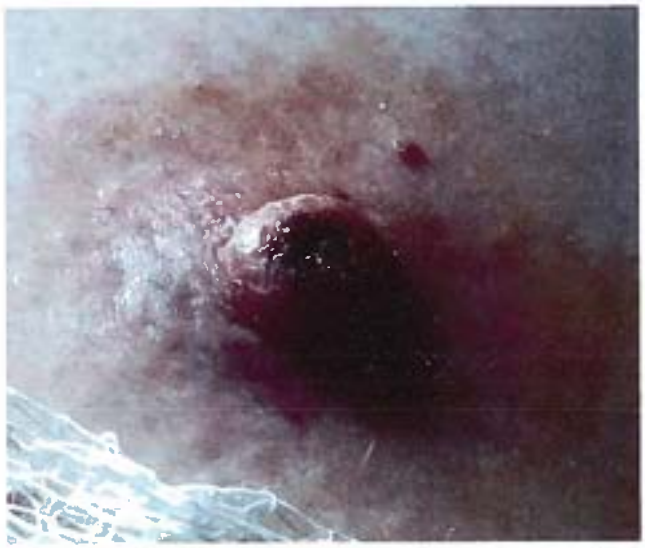
Keratoacanthoma is a **benign epithelial** tumour.
They are more frequent in **middle age** and do not become more common in old age (unlike basal cell and squamous cell carcinoma).

### Features - said to look like a volcano or crater:

- Initially a smooth dome-shaped papule.
- **Rapidly grows** to become a **crater centrally-filled with keratin.**

**Spontaneous** regression of Keratoacanthoma **within 3 months** is common, often resulting in a **scar**.

Whilst Keratoacanthoma is a benign lesion, such lesions should however be **urgently excised** as **it is difficult clinically to exclude squamous cell carcinoma**. Removal also may prevent scarring, so **urgent referral to the dermatologist.**



## Malignant melanoma

There are four main subtypes of melanoma. Nodular melanoma is the most aggressive whilst the other forms spread more slowly.

| | Superficial spreading | Nodular | Lentigo maligna | Acral lentiginous |
|---|---|---|---|---|
| **Frequency** | 70% of cases | Second commonest | Less common | Rare form |
| **Typically affects** | Arms, legs, back and chest, young people | Sun exposed skin, middle-aged people | Chronically sun-exposed skin, older people | Nails, palms or soles, African Americans or Asians |
| **Appearance** | A growing moles with diagnostic features listed above | Red or black lump or lump which bleeds or oozes | A growing mole with diagnostic features listed above | Subungual pigmentation (Hutchinson's sign) or on palms or feet |

There are other rare forms of melanoma including desmoplastic melanoma, amelanotic melanoma, or melanoma arising in other parts of the body such as ocular melanoma.

| The main diagnostic features (major criteria): | Secondary features (minor criteria) |
|---|---|
| • Change in size<br>• Change in shape<br>• Change in colour | • Diameter >= 7mm<br>• Inflammation<br>• Oozing or bleeding<br>• Altered sensation |

## Treatment

- Suspicious lesions should undergo excision biopsy. The lesion should be removed in completely as incision biopsy can make subsequent histopathological assessment difficult.
- Once the diagnosis is confirmed the pathology report should be reviewed to determine whether further re-excision of margins is required (see below):

### Margins of excision-Related to Breslow thickness

| | |
|---|---|
| **Lesions 0-1mm thick** | 1cm |
| **Lesions 1-2mm thick** | 1- 2cm (Depending upon site and pathological features) |
| **Lesions 2-4mm thick** | 2-3 cm (Depending upon site and pathological features) |
| **Lesions >4 mm thick** | 3cm |

Further treatments such as sentinel lymph node mapping, isolated limb perfusion and block dissection of regional lymph node groups should be selectively applied.

## Malignant melanoma: prognostic factors

The primary **risk factors** for melanoma includes:

- Exposure to **ultraviolet** radiation (sun).
- Geographic location in a **sunny climate located near the equator**.
- **Fair** skinned individuals
- Increasing age, particularly **men** > 50 years.
- A personal or **family history** of a 1 st degree relative with melanoma.
- **Dyspiastic** naevi.
- **Greater than 50** naevi **2 mm or more** in diameter.
- **Xeroderma pigmentosum**
- **Familial atypical mole melanoma syndrome**.

The **invasion depth** of a tumour (Breslow depth) is the single most important factor in determining prognosis of patients with malignant melanoma.

**Melanoma >>> the invasion depth of the tumour** is the **single most** important **prognostic factor**

| Breslow Thickness | Approximate 5 year survival |
|---|---|
| < 1 mm | 95-100% |
| 1 - 2 mm | 80-96% |
| 2.1 - 4 mm | 60-75% |
| > 4 mm | 50% |

## Molluscum contagiosum

- Molluscum contagiosum is caused by **a pox virus (DNA)** infection.
- It is typically seen in **younger children** and results in **characteristic small, pearly, umbilicated (central dimple)** lesions.
- Molluscum contagiosum is **highly infectious**.
- Lesions **may be present for up to 12 months** and usually **resolve spontaneously**.
- Whilst various treatments may be effective in removing the lesions (e.g. surgery, cryotherapy, topical agents) **no treatment is recommend** in the **initial** phase due to the benign nature of the condition.

# Mycosis fungoides

Mycosis fungoides is a rare form of T-cell lymphoma that affects the skin.

## Features

- itchy, red patches which are<="" span="" style="box-sizing: border-box;">
- lesions tend to be of different colours in contrast to eczema/psoriasis where there is greater homogenicity

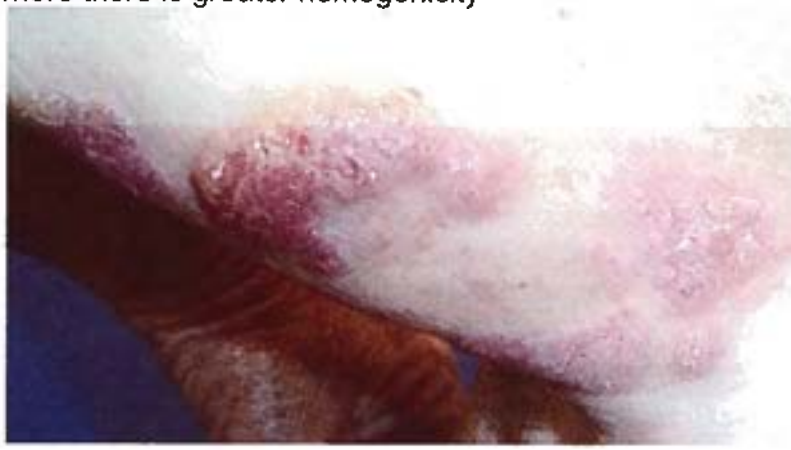


Image showing the plaque stage of mycosis fungoides

Further image showing the plaque stage of mycosis fungoides

## Myxoid cyst (mucous cysts)

They are **benign ganglion cysts** usually found on the **distal**, **dorsal** aspect of the **finger**. It is firm dome-shaped swelling. There is usually **osteoarthritis** in the surrounding joint. They are more common in **middle**-aged **women**.

## Onycholysis

Onycholysis describes **the separation of the nail plate from the nail bed**.

### Causes:

- Idiopathic
- Trauma e.g. Excessive manicuring
- Infection: especially fungal
- Skin disease: psoriasis, dermatitis
- Impaired peripheral circulation e.g. **Raynaud's**
- Systemic disease: hyper- and hypothyroidism
- **Tetracycline**

## Otitis externa

Otitis externa is a common reason for primary care attendance in the UK.

### Causes of otitis externa include:

- Infection: bacterial (Staphylococcus aureus, Pseudomonas aeruginosa) or fungal.
- Seborrhoeic dermatitis.
- Contact dermatitis (allergic and irritant).

### Features:

- Ear pain, itch, discharge.
- Otoscopy: red, swollen, or eczematous canal.

The recommend initial management of otitis externa is:

- **Topical antibiotic** or **a combined topical antibiotic with steroid.**
- **If** the **tympanic membrane is perforated aminoglycosides** are traditionally **not** used, **but** many ENT doctors **disagree** with this and feel that concerns about ototoxicity are unfounded.
- **If** there is **canal debris** then consider **removal**.
- If the canal is extensively swollen then an ear wick is sometimes inserted.

### Second line options include:

- Consider contact dermatitis secondary to neomycin.
- Oral antibiotics if the infection is spreading.
- Taking a swab inside the ear canal.
- Empirical use of an antifungal agent.

**Malignant otitis externa** is more common in **elderly diabetics**. In this condition there is extension of infection into the **bony** ear canal and the soft tissues deep to the bony canal. **Intravenous antibiotics** may be required.

## Parvovirus B19

Parvovirus B19 is a **DNA** virus which causes a variety of clinical presentations.
It was identified in the **1980's** as the cause of **erythema infectiosum**.

### Erythema infectiosum (also known as **fifth disease** or **'slapped-cheek syndrome'**):

- Most common presenting illness.
- Systemic symptoms: lethargy, fever, headache.
- 'Slapped-cheek' rash spreading to proximal arms and extensor surfaces.

### Other presentations:

- Asymptomatic.
- **Pancytopaenia** in immunosuppressed patients.
- **Aplastic crises** e.g. **in sickle-cell disease** (parvovirus B19 suppresses erythropoiesis for about a week so aplastic anaemia is rare unless there is a chronic haemolytic anaemia).

## Pellagra

Pellagra is a caused by **nicotinic acid (niacin) deficiency**.
The classical features are the **3 D's** - **D**ermatitis, **D**iarrhoea and **D**ementia.

Pellagra may occur as a consequence of **isoniazid therapy** (isoniazid inhibits the conversion of tryptophan to niacin) and it is more common in **alcoholics**.

### Features:

- **D**ermatitis (red-brown, symmetrically scaly rash on sun-exposed sites - termed Casal's necklace if around neck).
- **D**iarrhoea.
- **D**ementia, depression.
- **D**eath if not treated.

## Pityriasis rosea

### Overview:

- Cause unknown, herpes hominis virus 7 (HHV-7) a possibility.
- Tends to affect **young adults.**

### Features:

- **Herald patch** (usually on **trunk**).
- Followed by **erythematous, oval, flat scaly patches** which follow a **characteristic distribution** with the longitudinal diameters of the oval lesions **running parallel** to the line of Langer. This may produce **a 'fir-tree' appearance.**

### Management:

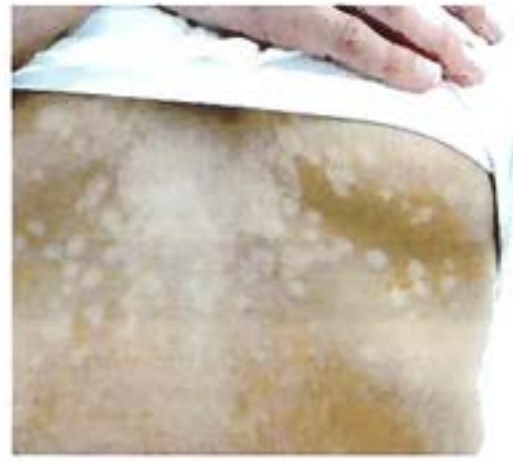
- Self-limiting, usually disappears after 4-6 weeks.

## Pityriasis versicolor

Pityriasis versicolor, also called **tinea versicolor**, is a superficial cutaneous fungal infection caused by Malassezia furfur (formerly termed Pityrosporum ovale).

### Features:

- Most commonly affects **trunk**
- **Patches** may be **hypo pigmented**, **pink or brown** (hence **versicolor**)
- **Scale** is common
- Mild pruritus



### Predisposing factors:

- Occurs in **healthy** individuals
- Immunosuppression
- Malnutrition
- Cushing's

### Management

- topical antifungal. NICE Clinical Knowledge Summaries advise **ketoconazole shampoo** as this is more cost effective for large areas
- **Topical selenium sulphide**
- if failure to respond to topical treatment then consider alternative diagnoses (e.g. send scrapings to confirm the diagnosis) + oral itraconazole

# Pemphigus vulgaris

Pemphigus vulgaris is an **autoimmune** disease caused by **antibodies** directed against **desmoglein 3**, a cadherin-type epithelial cell adhesion molecule.
It is more common in the Ashkenazi Jewish population.

**Blisters/bullae:**

- No mucosal involvement (in exams at least) >>> **Bullous Pemphigoid**
- Mucosal involvement >>> **Pemphigus vulgaris**

## Features:

- **Mucosal ulceration is common and often the presenting symptom**. **Oral** involvement is seen in 50-70% of patients.
- **Skin blistering - flaccid, easily ruptured** vesicles and bullae. Lesions are typically **painful** but **not itchy**. These may develop months after the initial mucosal symptoms. Nikolsky's describes the spread of bullae following application of horizontal, tangential pressure to the skin.
- Acantholysis on biopsy.

## Management:

- steroids are first-line
- Immunosuppressants.

## Pompholyx

Pompholyx is a type of **eczema** which affects both the **hands** (**cheiro**pompholyx) and the **feet** (**pedo**pompholyx).
It is also known as dyshidrotic eczema or vesicular eczema.

### Features:

- Small **blisters** on the **palms** and **soles**.
- **Pruritic**, sometimes burning sensation.
- Once blisters burst skin may become dry and crack.

### Management:

- Cool compresses
- Emollients
- Topical steroids

# Pruritus

## The most important causes of pruritus:

- **Iron deficiency anaemia.**
- **Polycythaemia.**
- **Liver disease.**
- **Chronic kidney disease.**
- **Lymphoma.**

## Other causes:

- **Hyper- and hypothyroidism**
- **DM**
- **Pregnancy**
- **'Senile' pruritus**
- **Urticaria**
- **Skin** disorders: **eczema**, **scabies**, psoriasis, **Pityriasis rosea**

# Psoriasis

Psoriasis is a common (prevalence around 2%) and chronic skin disorder.
It generally presents with red, scaly patches on the skin although it is now recognised that patients with psoriasis are at increased risk of arthritis and cardiovascular disease.

## Pathophysiology:

- Multifactorial and not yet fully understood
- Genetic: associated HLA-B13, -B17, and -Cw6. Strong concordance (70%) in identical twins.
- Immunological: **abnormal T cell activity** stimulates **keratinocyte proliferation.** There is increasing evidence this may be mediated by a novel group of T helper cells producing **IL-17**, designated Th17. These cells seem to be a third T-effector cell subset in addition to **Th1** and Th2. (**Psoriasis is mediated by type 1 helper T cells** which are involved in **the cell mediated response**, rather than type 2 helper T cells).
- Environmental: it is recognised that psoriasis may be worsened (e.g. Skin trauma, stress), triggered (e.g. Streptococcal infection) or improved (e.g. Sunlight) by environmental factors.

## Recognised subtypes of psoriasis:

- **Plaque psoriasis**: the **most common** sub-type resulting in the typical well demarcated red, scaly patches affecting the **extensor** surfaces, sacrum and scalp. **Scalp psoriasis may occur in isolation in patients with no history of psoriasis elsewhere.**
- **Flexural psoriasis**: in contrast to plaque psoriasis the skin is smooth.
- **Guttate psoriasis**: transient psoriatic rash frequently triggered by a streptococcal infection. Multiple red, teardrop lesions appear on the body.
- **Pustular psoriasis**: commonly occurs on the palms and soles.
- **Erythrodermic psoriasis**:
  - May result from progression of chronic disease to an **exfoliative** phase with plaques covering **most** of the body. Associated with mild systemic upset.
  - More serious form is an acute deterioration. This may be triggered by a variety of factors such as withdrawal of systemic steroids. Patients need to be admitted to hospital for management.

## Other features:

- **Nail** signs: **pitting**, **Onycholysis**
- **Arthritis**

## Complications:

- **Psoriatic arthropathy** (around **10%**): **Psoriatic arthropathy may occur prior to the development of skin lesions.**
- Increased incidence of metabolic syndrome
- **Increased incidence of cardiovascular disease**
- Increased incidence of venous thromboembolism
- Psychological distress

# Psoriasis: management

NICE released guidelines on the management of psoriasis and psoriatic arthropathy.

## Chronic plaque psoriasis:

- Regular emollients may help to reduce scale loss and reduce pruritus.
- **First**-line: NICE recommend a **potent corticosteroid applied once daily** plus **vitamin D analogue (Calcipotriol) applied once daily** (applied separately, one in the morning and the other in the evening) **for up to 4 weeks** as **initial** treatment.
- Second-line: if no improvement after 8 weeks then offer a vitamin D analogue twice daily.
- Third-line: if no improvement after 8-12 weeks then offer either: a potent corticosteroid applied twice daily for up to 4 weeks or a **coal tar** preparation applied once or twice daily.
- Short-acting **dithranol** can also be used.

1st line treatment of psoriatic **plaques** is >> **Topical steroid + topical Calcipotriol**

### Scalp psoriasis:

- NICE recommend the use of **potent topical corticosteroids** used once daily for 4 weeks.
- If no improvement after 4 weeks then either use **a different formulation** of the potent corticosteroid (for example, a shampoo or mousse) and/or a **topical agents to remove adherent scale (for example, agents containing salicylic acid, emollients and oils)** before application of the potent corticosteroid.

### Face, flexural and genital psoriasis:

- NICE recommend offering a mild or moderate potency corticosteroid applied once or twice daily for a maximum of 2 weeks.
- Topical Calcipotriol is usually irritant in flexures.
- Mild tar preparations are an option but may be messy and cumbersome.

**Flexural** psoriasis **>>> topical steroid**

### Steroids in psoriasis:

- **Topical steroids** are commonly used in **flexural** psoriasis and there is also a role for mild steroids in facial psoriasis.

- If steroids are ineffective for these conditions **vitamin D analogues** or **Tacrolimus ointment** should be used second line.
- Pts. should have **4 week breaks between** courses of topical steroids.
- **Very potent steroids should not be used for longer than 4 weeks** at a time. **Potent steroids can be used for up to 8 weeks at a time**.
- The scalp, face and flexures are particularly prone to steroid atrophy so topical steroids should not be used for more than 1-2 weeks/month

### Secondary care management:

#### 1) Phototherapy:

- **Narrow band ultraviolet B light** is now the treatment of choice. If possible this should be given 3 times a week.
- **Photo-chemotherapy** is also used - **Psoralens** + **Ultraviolet A light (PUVA).**
- Adverse effects: skin ageing, **squamous cell cancer (NOT melanoma**).

#### 2) Systemic therapy:

- **Oral methotrexate** is used **first**-line. It is particularly useful if there is associated joint disease.
- **Cyclosporine.**
- **Systemic Retinoids.**
- **Biological** agents: infliximab, etanercept and adalimumab.
- **Ustekinumab** (IL-12 and IL-23 blocker) is showing promise in early trials.

### Mechanism of action of commonly used drugs:

- **Coal tar:** probably inhibit DNA synthesis. It is smelly and messy - most patients would not tolerate facial application.
- **Calcipotriol**: vitamin D analogue which reduces epidermal proliferation and restores a normal horny layer. Calcipotriol is not recommended for facial lesions as it may cause irritation - calcitriol and tacalcitol are alternatives.
- **Dithranol**: inhibits DNA synthesis, wash off after 30 mins, SE: burning, staining.

### The following factors may exacerbate psoriasis:

- **Trauma.**
- **Alcohol.**
- **Drugs**: (Reactions may occur from less than 1 month to 1 year after the medication is initiated):
  - **Beta blockers,**
  - **ACEIs,**
  - **Lithium,**

  - **Antimalarials** (**chloroquine** and hydroxychloroquine) and
  - **NSAIDs.**
- **Withdrawal of systemic steroids.**

**NB**: Precipitation of the rash may take **up to a year to develop after** initiation of the medications.
**NB**: It is still difficult to establish the link between anti-malarial and psoriasis exacerbation.
**NB**: Lithium prescription with ACEI is not recommended due to the problem of a significant increase in serum Lithium levels.
**NB**: The **safest** treatment - that which produces the best clinical effect with minimal side effects >>> Psoralen and ultraviolet light (**PUVA**).
**NB**: **Oral steroids are contraindicated in psoriasis** and although one may see an initial improvement, a very serious rebound effect may be seen.

**MRCPUK part 1 exam: Which medication is of most concern with respect to worsening of psoriasis? >> Atenolol**

## Psoriasis: guttate

**Guttate psoriasis** is more common in **children and adolescents**.
It may be precipitated by a **streptococcal** infection (sore throat/tonsillitis) **2-4 weeks prior** to the lesions appearing.

### Features

- tear drop papules on the trunk and limbs
  - *gutta* is Latin for drop
  - pink, scaly patches or plques of psoriasis
- tends to be acute onset over days

### Management:

- Most cases resolve **spontaneously** within 2-3 months
- There is **no** firm evidence to support the use of antibiotics to eradicate streptococcal infection.
- Topical agents as per psoriasis
- UVB phototherapy
- Tonsillectomy may be necessary with recurrent episodes

## Differentiating guttate psoriasis and pityriasis rosea

| | Guttate psoriasis | Pityriasis rosea |
|---|---|---|
| **Prodrome** | Classically preceded by a streptococcal sore throat 2-4 weeks | Many patients report recent respiratory tract infections but this is not common in questions |
| **Appearance** | 'Tear drop', scaly papules on the trunk and limbs | Herald patch followed 1-2 weeks later by multiple erythematous, slightly raised oval lesions with a fine scale confined to the outer aspects of the lesions.<br>May follow a characteristic distribution with the longitudinal diameters of the oval lesions running parallel to the line of Langer. This may produce a 'fir-tree' appearance |
| **Treatment / natural history** | Most cases resolve spontaneously within 2-3 months<br>Topical agents as per psoriasis<br>UVB phototherapy | Self-limiting, resolves after around 6 weeks |

# Porphyria cutanea tarda

Porphyria cutanea tarda is **the most common hepatic porphyria**.
It is due to an inherited defect in uroporphyrinogen decarboxylase or caused by hepatocyte damage e.g. alcohol, hepatitis C, oestrogens.

## Features:

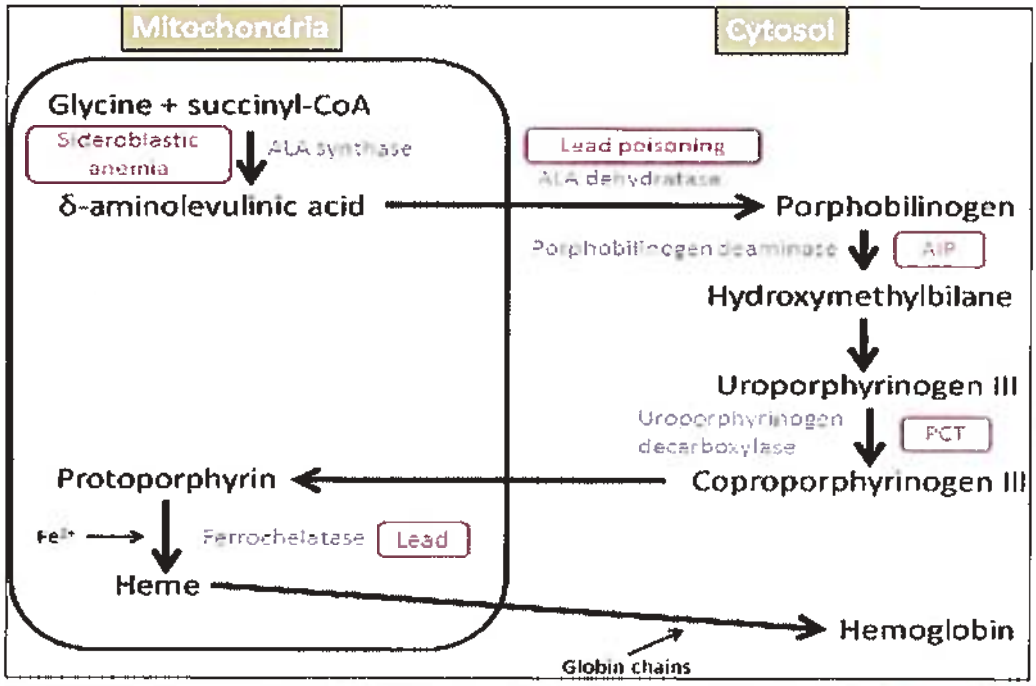
- Classically presents with **photosensitive rash** with **blistering** and skin **fragility (extremely fragile and tears easily)** on the **face** and **dorsal aspect of hands** (most common feature).
- **Hypertrichosis.**
- **Hyperpigmentation.**

**Porphyria cutanea tarda:**
- Blistering photosensitive rash
- Hypertrichosis
- Hyperpigmentation

**Investigations:** Urine: elevated uroporphyrinogen and pink fluorescence of urine under Wood's lamp.

## Management:

- Chloroquine
- Venesection



# Photosensitive skin disorders

## Diseases aggravated by exposure to sunlight:

- **SLE, discoid lupus.**
- **Porphyria cutanea tarda** (**NOT acute intermittent Porphyria**).
- **Herpes labialis** (cold sores).
- **Pellagra.**
- **Xeroderma pigmentosum.**
- Solar urticaria.
- Polymorphic light eruption.

# Pressure ulcers

**Waterlow score - used to identify patients at risk of pressure sores**

## Overview

- Pressure ulcers develop in patients who are unable to move parts of their body due to illness, paralysis or advancing age.
- They typically develop over bony prominences such as the sacrum or heel. The following factors predispose to the development of pressure ulcers:
  - malnourishment
  - incontinence
  - lack of mobility
  - pain (leads to a reduction in mobility)
- The **Waterlow score** is widely used to screen for patients who are at risk of developing pressure areas. It includes a number of factors including body mass index, nutritional status, skin type, mobility and continence.

### Grading of pressure ulcers

the following is taken from the European Pressure Ulcer Advisory Panel classification system.

| Grade | Findings |
|---|---|
| **Grade 1** | Non-blanchable erythema of intact skin. Discolouration of the skin, warmth, oedema, induration or hardness may also be used as indicators, particularly on individuals with darker skin |
| **Grade 2** | Partial thickness skin loss involving epidermis or dermis, or both. The ulcer is superficial and presents clinically as an abrasion or blister |

| | |
|---|---|
| **Grade 3** | Full thickness skin loss involving damage to or necrosis of subcutaneous tissue that may extend down to, but not through, underlying fascia. |
| **Grade 4** | Extensive destruction, tissue necrosis, or damage to muscle, bone or supporting structures with or without full thickness skin loss |

### Management

- a moist wound environment encourages ulcer healing. Hydrocolloid dressings and hydrogels may help facilitate this. The use of soap should be discouraged to avoid drying the wound
- wound swabs should not be done routinely as the vast majority of pressure ulcers are colonised with bacteria. The decision to use systemic antibiotics should be taken on a clinical basis (e.g. Evidence of surrounding cellulitis)
- consider referral to the tissue viability nurse
- surgical debridement may be beneficial for selected wounds

## Pyogenic granuloma

### overview

- relatively common benign skin lesion
- benign vascular lesion of the skin and mucosa.
- The name is a double misnomer - the lesion is neither pyogenic nor a granuloma.
- There are multiple alternative names but perhaps 'eruptive haemangioma' is the most useful.
- Pathologically, it is an inflammatory lesion composed of granulation tissue and chronic inflammatory cells.

### Etiology:

- unknown,
- **associated with trauma and pregnancy**

### Epidemiology

- more common in women and young adults

### Features

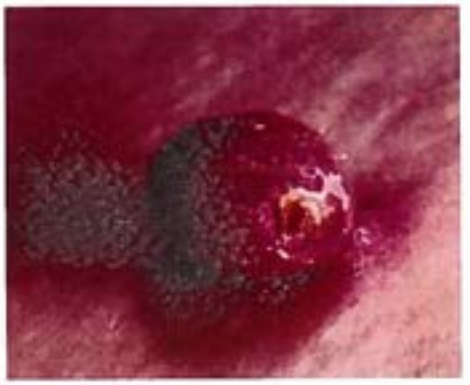
- initially soft, round, bright red spot
- usually solitary lesions,
- Lesions often grow rapidly (**over weeks**).
- **tender and bled easily when touched.**

## Localization:

- The most common location are:
  - fingers **(commonly involve the digits)**
  - mucosal surfaces of the mouth
  - inner surfaces of the nose.

## Treatment:

- lesions associated with pregnancy often resolve spontaneously post-partum
- other lesions usually persist.
- surgical excision
  - Removal methods include curettage and cauterisation, cryotherapy, excision



# Scabies

- Scabies is caused by the mite Sarcoptes scabiei and is spread by prolonged skin contact.
- It typically affects children and young adults.
- The scabies mite burrows into the skin, laying its eggs in the stratum corneum.
- The **intense pruritus** associated with scabies is due to a **delayed type IV hypersensitivity reaction** to mites/eggs which **occurs about 30 days after the initial infection.**

## Features:

- **Widespread pruritus**
  - **Scabies can present with an itchy dermatitic-looking rash on the body, but the clues are at certain sites (soles, genitalia, buttocks)**
- **Linear burrows** on **the side of fingers, interdigital webs and flexor aspects of the wrist**
  - **Burrows (linear crusted lesions of a few millimetres in length) are pathognomonic**
  - **It has a predilection for the web-spaces and around the nipples.**
- In infants the face and scalp may also be affected
- Secondary features are seen due to scratching: excoriation, infection

## Management:

- **Permethrin** 5% is **first**-line
- **Malathion** 0.5% is **second**-line
- Give appropriate guidance on use (see below)
- **Pruritus persists for up to 4-6 weeks post eradication**

### Patient guidance on treatment (from Clinical Knowledge Summaries):

- Avoid close physical contact with others until treatment is complete.
- **All household** and close physical contacts should **be treated at the same time, even if asymptomatic.**
- Launder, iron or tumble dry clothing, bedding, towels, etc., on the first day of treatment to kill off mites.

**The BNF advises to apply** the insecticide **to all areas**, including the **face** and **scalp**, contrary to the manufacturer's recommendation. Patients should be given the following instructions:

- Apply the insecticide cream or liquid to cool, dry skin.
- Pay close attention to areas between fingers and toes, under nails, armpit area, creases of the skin such as at the wrist and elbow.

- **Allow to dry and leave on the skin for 8-12 hours for Permethrin**, or **for 24 hours for Malathion, before washing off**.
- Reapply if insecticide is removed during the treatment period, e.g. If wash hands, change nappy, etc.
- **Repeat treatment 7 days later.**

**Scabies >>> Permethrin treatment: all skin including scalp + leave for 12 hours + retreat in 7 days.**

### Crusted (Norwegian) scabies:

- Crusted scabies is seen in pt. with suppressed immunity, especially **HIV**.
- The crusted skin will be teeming with hundreds of thousands of organisms.
- **Ivermectin** is the treatment of choice and isolation is essential.

## Seborrhoeic dermatitis in adults

Seborrhoeic dermatitis in adults is a **chronic dermatitis** thought to be caused by an inflammatory reaction related to a proliferation of a normal skin inhabitant, a fungus called Malassezia furfur (formerly known as Pityrosporum ovale).
It is common, affecting around 2% of the general population.

### Features:

- **Eczematous** lesions on the **sebum-rich areas**: **scalp** (may cause **dandruff**), periorbital, **auricular** and **nasolabial folds.**
- **Otitis externa** and **blepharitis** may develop.

The two complications that are most associated with seborrhoeic dermatitis are: **Otitis externa** and **blepharitis**.

## Associated conditions include:

- **HIV**
- **Parkinson's disease**

Seborrhoeic dermatitis is more common in patients with Parkinson's disease and patients with HIV.

## Scalp disease management:

- **Over the counter** preparations containing **zinc** pyrithione ('Head & Shoulders') and **tar shampoo** ('Neutrogena T/Gel') are **first**-line.
- The preferred **second**-line agent is **topical ketoconazole**.
- **Selenium sulphide shampoo** and **topical corticosteroid** may also be useful.

## Face and body management:

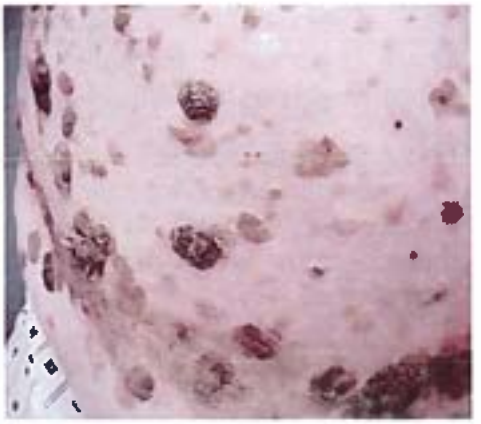
- Topical antifungals: e.g. Ketoconazole.
- Topical steroids: best used for short periods.
- Difficult to treat - **recurrences are common.**

There is less role for emollients / Aqueous cream in the management of seborrhoeic dermatitis than in other chronic skin disorders.

**EX:** A 67-year-old man with a history of Parkinson's disease presents due to the development of an itchy, red rash on his neck, behind his ears and around the nasolabial folds. He had a similar flare up last winter but did not seek medical attention. What is the most likely diagnosis? >> **Seborrhoeic dermatitis.**

## Seborrheic keratosis

- Seborrheic keratoses are the most common benign tumor in older individuals.
- and they develop from the proliferation of epidermal cells.
- No specific etiologic factors have been identified.
- Typical features include a warty and waxy surface with surface crypts and a stuck on appearance.
- They typically have an appearance of being stuck on the skin surface.
- Because they begin at a later age and can have a wart-like appearance, seborrheic keratoses are often called the "barnacles of aging.
- Most commonly they are several
- Can growths anywhere on the skin, except the palms and soles. Most often on the chest, back, head, or neck.
- Commonly used treatments include Curettage and cautery (C&C), and cryotherapy (for thinner lesions).



multiple seborrheic keratoses in an autosomally dominant mode of inheritance.

## Sezary syndrome

Sezary syndrome is a type of T-cell cutaenous lymphoma.

### Features

- pruritus
- erythroderma typically affecting the palms, soles and face
- atypical T cells
- lymphadenopathy
- hepatosplenomegaly

# Shin lesions

The differential diagnosis of shin lesions includes the following conditions:

- **Erythema nodosum**
- **Pyoderma gangrenosum**
- **Pretibial myxoedema**
- **Necrobiosis lipoidica diabeticorum**

## Below are the characteristic features:

## 1) Erythema nodosum (EN):

### Overview:

- **Inflammation of subcutaneous fat**.
- Typically causes **symmetrical**, **tender**, **erythematous**, **nodular** lesions.
- Usually occurs over shins, may also occur elsewhere (e.g. forearms, thighs).
- It is **self-limiting** and usually **resolves within 6 weeks.**
- Lesions **heal without scarring**.
- Sometimes in severe cases **Colchicine (SE: diarrhoea)**, **Thalidomide (teratogenic)**, Dapsone, Corticosteroids, or K iodide can be used.

**Erythema nodosum (EN)>> Heal without scarring within 1-2 months (6 week)**

Thalidomide is secreted in **semen**, so the **male** should use **barrier** contraception until at least 1 week after cessation of ttt.

**Woman** must provide a pregnancy test 24 hrs prior to beginning thalidomide therapy because of the very great risk of **teratogenicity**.

If male take thalidomide >>> so he should use barrier contraception and his wife should use effective contraception also.

### Causes:

- **Infection**: **Streptococci**, **TB**, **Histoplasmosis**, **Brucellosis**, **Campylobacter.**
- **Systemic** disease: **Sarcoidosis**, **IBD** (UC/CD), **Behcet's**.
- **Malignancy/lymphoma.**
- **Drugs**: **Penicillins**, **Sulphonamides**, **combined OCP.**
- **Pregnancy.**

- Apart from the **chest x ray**, the following are also important:

- A throat culture
- Antistreptolysin-O test (ASOT)
- Mantoux test

The commonest cause of EN is streptococcal infection.

**EX:** A 35-year-old female presents tender, erythematous nodules over her forearms with elevated serum calcium level >>>> think of sarcoidosis.

Pt with EN >>> the most useful next investigation is >>> **chest x-ray** as it helps exclude **sarcoidosis** and **tuberculosis**, the two most important cause of EN.

## 2) Pyoderma gangrenosum:

### Features:

- Typically on the **lower limbs.**
- Initially **small red papule.**
- Later **deep**, **red**, **necrotic ulcers** with a **violaceous border.**
- May be accompanied systemic symptoms e.g. Fever, myalgia.

### Causes

- **Idiopathic** in **50%**, may **also be seen in:**
- **GIT:**
  - **Inflammatory bowel disease**: **ulcerative** colitis, Crohn's.
  - **Primary sclerosing cholangitis**
  - **Primary biliary cirrhosis.**
- **Connective tissue disorders:** **RA** and **SLE.**

### 3) Infection:
- Candidiasis
- Staphylococcal

### 4) Neuropathic ulcers
### 5) Vitiligo
### 6) Lipoatrophy

## Skin disorders associated with pregnancy

### Atopic eruption of pregnancy
- is the commonest skin disorder found in pregnancy
- it typically presents as an eczematous, itchy red rash.
- no specific treatment is needed

### Polymorphic eruption of pregnancy (see picture)
- Pruritic condition associated with last trimester
- Lesions often first appear in abdominal striae
- Management depends on severity: emollients, mild potency topical steroids and oral steroids may be used

### Pemphigoid gestationis: (see picture)
- Pruritic **blistering** lesions.
- Often develop in **peri-umbilical region**, later **spreading** to the trunk, back, buttocks and arms.
- Usually presents 2nd or 3rd trimester and is **rarely seen in the first pregnancy.**
- **Oral corticosteroids** are usually required.

## Skin disorders associated with tuberculosis

### Possible skin disorders:

- **Lupus vulgaris** (**accounts for 50% of cases**) (see pic)
- **Erythema nodosum**
- **Scarring alopecia**
- **Scrofuloderma**: breakdown of skin overlying a tuberculous focus
- **Verrucosa cutis**
- **Gumma**

Lupus vulgaris is the most common form of cutaneous TB seen in the Indian subcontinent. It generally occurs on the face and is common around the nose and mouth. The initial lesion is an **erythematous flat plaque** which gradually becomes **elevated** and may **ulcerate** later.

## Skin disorders associated with malignancy

Paraneoplastic syndromes associated with internal malignancies:

| Skin disorder | Associated malignancies |
|---|---|
| Acanthosis nigricans | GIT, Gastric cancer |
| Acquired ichthyosis | Lymphoma |
| Acquired hypertrichosis lanuginosa | Gastrointestinal and lung cancer |
| Dermatomyositis | Lung and Ovarian cancer |
| Erythema gyratum repens | Solid organ malignancies such as Lung cancer & Breast cancer. |
| Erythroderma | Lymphoma |
| Migratory thrombophlebitis | Pancreatic cancer |
| Necrolytic migratory erythema | Glucagonoma |
| Pyoderma gangrenosum (bullous and non-bullous forms) | Myeloproliferative disorders |
| Sweet's syndrome (also known as acute febrile neutrophilic dermatosis) | Haematological malignancy e.g. Myelodysplasia, AML - tender, purple plaques |
| Tylosis | Oesophageal cancer |

- Haematological malignancy:
  - **Myeloproliferative disorders**.
  - **Lymphoma**, myeloid **leukaemias**.
  - **Monoclonal gammopathy (IgA).**

**Management**

- The potential for **rapid progression is high** in most patients and most doctors advocate **oral steroids (prednisolone) as first-line treatment**.
- Other immunosuppressive therapy, for example cyclosporine and infliximab, have a role in difficult cases.

Note whilst Pyoderma gangrenosum can occur in DM it is rare and is generally not included in a differential of potential causes.

**EX**: A 34-year-old man with a history of polyarthralgia, back pain and diarrhoea is found to have a 3 cm red lesion on his shin which is starting to ulcerate. What is the most likely diagnosis? >>> **Ulcerative colitis**, which has a known association with large-joint arthritis, sacroilitis and **Pyoderma gangrenosum**.

## 3) Pretibial myxoedema:

- Symmetrical, erythematous lesions seen in **Graves'** disease.
- **Shiny**, **orange peel** skin.

## 4) Necrobiosis lipoidica diabeticorum:

- **Shiny**, **painless** areas of **yellow**/red skin on the shin of diabetics.
- Often associated with **telangiectasia.**

# Skin disorders associated with diabetes

Note whilst Pyoderma gangrenosum can occur in DM it is rare and is often not included in a differential of potential causes.

## 1) Necrobiosis lipoidica diabeticorum:

- Shiny, **painless** areas of yellow/red/brown skin typically on the shin.
- Often associated with surrounding **telangiectasia.**
- It is seen in 0.3-1% of patients with DM.
- The exact cause of necrobiosis lipoidica is unknown, but the leading theory of necrobiosis lipoidica has focused on diabetic microangiopathy.
- Around 40-60% of patients with Necrobiosis lipoidica have DM and the condition may pre-date the development of abnormal blood sugar.
- More common in females.
- Biopsy: **granuloma** formation with infiltration of lymphocytes, plasma cells and eosinophils.
- Treatment : **Topical / injectable steroids**, skin grafting ± camouflage creams.

## 2) Granuloma annulare: (see pic)

- **Papular** lesions that are often **slightly hyperpigmented** and **depressed centrally.**
- Typically occur on the **dorsal** surfaces of the **hands and feet**, and on the extensor aspects of the arms and legs (**shin**).
- It is not clear from recent studies if there is actually a significant association between DM and granuloma annulare, but it is often listed in major textbooks.

## Solar keratosis

- hyperkeratotic lesion with underlying erythema.
- bleed when scratched
- Progression of these lesions to squamous cell skin cancer is slow,
- **Topical 5-FU cream** used twice a day for 3–4 weeks usually achieves clearance of the lesion.
- Diclofenac gel requires a more prolonged treatment period (up to 12 weeks), meaning that it is the second-choice option for compliance reasons. It is useful where coverage of a larger area of skin is required.

solar keratosis (on scalp of elderly)

## Spider nevi

most common on the face and upper chest.
typically asymptomatic
usually resolve spontaneously.

### Causes

#### chronic liver disease

- the presence of more than five lesions is likely to be due to chronic liver disease.
- may resolve when liver function increases or when a liver transplant is performed.
- **the cause of the spider nevi >> patients cannot metabolize circulating estrogen**
- pregnancy
  - may resolve after childbirth.
- oral contraceptives,
  - may resolve after stopping the contraceptives.

forehead lesion (spider nevus (nevus araneus))

## Squamous cell carcinoma of the skin

Squamous cell carcinoma is a common variant of skin cancer. Metastases are rare but may occur in 2-5% of patients.

### Risk factors include:

- excessive exposure to sunlight / psoralen UVA therapy
- actinic keratoses and Bowen's disease
- immunosuppression e.g. following **renal transplant, HIV**
- smoking
- long-standing leg ulcers (Marjolin's ulcer)
- genetic conditions e.g. xeroderma pigmentosum, oculocutaneous albinism

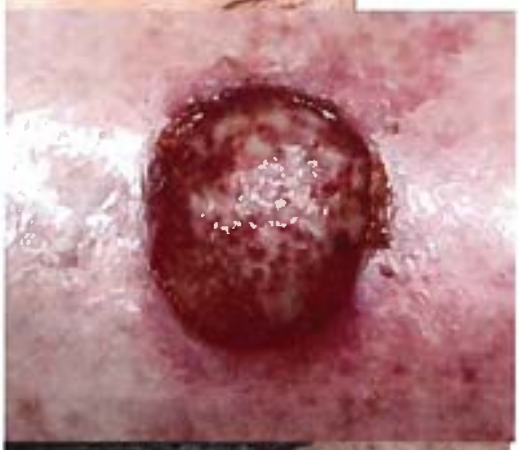
### Treatment

Surgical excision with 4mm margins if lesion <20mm in diameter. If tumour >20mm then margins should be 6mm. Mohs micrographic surgery may be used in high-risk patients and in cosmetically important sites.

### Prognosis

| Good Prognosis | Poor prognosis |
|---|---|
| Well differentiated tumours | Poorly differentiated tumours |
| <20mm diameter | >20mm in diameter |
| <2mm deep | >4mm deep |
| No associated diseases | Immunosupression for whatever reason |

## Image gallery



## Stevens-Johnson syndrome (SJS)

Stevens-Johnson syndrome is the **severe** form of **erythema multiforme** associated with **mucosal** involvement and **systemic** symptoms.

### Features:

- **Rash** is typically **maculopapular** with **target lesions** being characteristic. May develop into vesicles or bullae.
- **Mucosal** involvement.
- **Systemic** symptoms: fever, arthralgia.

### Causes

- penicillin
- **sulphonamides**
- lamotrigine, carbamazepine, phenytoin
- allopurinol
- NSAIDs
- oral contraceptive pill

### Management

- hospital admission is required for supportive treatment

The antibiotic which is most associated with the development of Stevens-Johnson syndrome is >>> **Sulphonamides (Co-trimoxazole).**

## Systemic mastocytosis

Systemic mastocytosis results from **a neoplastic proliferation** of **mast cells.**

### Features:

- **Urticaria pigmentosa** - produces a wheal on rubbing (Darier's sign).
- **Flushing.**
- **Abdominal pain.**
- **Monocytosis** on the blood film.

### Diagnosis:

- ↑ **Serum tryptase** levels.
- ↑ **Urinary histamine**.

**EX**: A 17-year-old man presents with a 2 week history of abdominal pain, diarrhoea and repeated episodes of flushing. Examination reveals urticarial skin lesions on the trunk. >>> **Systemic mastocytosis** >>> ↑ **Urinary histamine**.

**NB:**

- Given the history of diarrhoea and flushing a diagnosis of **carcinoid syndrome** should be considered, which would be investigated with **urinary 5-HIAA levels**. This would not however explain the urticarial skin lesions.
- **In a young person a diagnosis of systemic mastocytosis should be considered**.
- Another factor against carcinoid syndrome is the age of the patient - the average **age** of a patient with a **carcinoid** tumour is **61** years.

## Tinea

Tinea is a term given to Dermatophytes fungal infections.
Three main types of infection are described depending on what part of the body is infected:

- Tinea **capitis** - scalp
- Tinea **corporis** - trunk, legs or arms
- Tinea **pedis** - feet

### Tinea capitis (scalp ringworm):

- **A cause** of **scarring alopecia** mainly seen in **children.**
- If untreated a raised, pustular, spongy/boggy mass called a **kerion** may form.
- **Most common cause** is **Trichophyton tonsurans** in the UK and the USA.
- May also be caused by **Microsporum canis** acquired from cats or dogs.
- **Diagnosis:**
  - The most useful investigation is **scalp scrapings.**
  - Lesions due to Microsporum canis green fluorescence under Wood's lamp.
  - Lesions due to Trichophyton species do not readily fluoresce under Wood's lamp.
- **Management** (based on CKS guidelines):
  - **Oral antifungals**:
    - **Terbinafine** for Trichophyton tonsurans infections and
    - **Griseofulvin** for Microsporum infections.
  - **Topical ketoconazole shampoo** should be given for **the first two weeks** to reduce transmission.

Image showing a kerion

## Tinea corporis:

- Causes include **Trichophyton rubrum** and **Trichophyton verrucosum** (e.g. from contact with cattle).
- Well-defined annular, erythematous lesions with pustules and papules.
- May be treated with **oral fluconazole**.

## Tinea pedis (athlete's foot):

- Characterised by itchy, peeling skin between the toes.
- Common in adolescence.

## Tinea incognito

- **What is the cause for tinea incognito?**
  - **Inappropriate treatment with steroid cream**
- Tinea incognito is the name given to tinea when the clinical appearance has been altered by inappropriate treatment, usually a topical steroid cream
- The result is that the original infection slowly extends Often the patient and/or their doctor believe they have a dermatitis, hence the use of a topical steroid cream
- The steroid cream dampens down inflammation so the condition feels less irritable But when the cream is stopped for a few days the itch gets worse, so the steroid cream is promptly used again
- The more steroid applied, the more extensive the fungal infection becomes

# Toxic epidermal necrolysis (TEN)

TEN is a **potentially life-threatening skin disorder** that is most commonly seen secondary to an **idiosyncratic drug reaction**.
It is a severe **mucocutaneous exfoliative** disease with an **uncertain** pathogenesis and a **high mortality rate**.
Patients present with **erythematous**-to-**dusky** plaques and **targetoid** lesions that progress rapidly to **painful**, **full-thickness**, epidermal desquamation involving **more than 30% of body surface area (face, trunk & limbs)**. **Mucosal** involvement is also seen.
In this condition the skin develops a **scalded** appearance over an **extensive area**. Some authors consider TEN to be **the severe end of a spectrum** of skin disorders which includes **erythema multiforme** and **Stevens-Johnson syndrome.**

## Features:

- Systemically unwell e.g. **pyrexia**, tachycardia
- **Diffuse** erythematous, **painful rash** with evidence of some lateral sliding of these erythematous areas on palpation.
- **Positive Nikolsky's sign**: **the epidermis separates** with **mild lateral pressure.**

## Causes:

- **Viral** infections.
- **Leukaemia** and **lymphoma**.
- **Drugs** known to induce TEN:
  - **Phenytoin**
  - **Carbamazepine**
  - **Penicillins**
  - **Sulphonamides**
  - **Allopurinol**
  - **NSAIDs**

## Management:

- **Stop** precipitating factor.
- Supportive care, often in ICU.
- **IVIG** Intravenous immunoglobulin has been shown to be effective and is now commonly used **first**-line.
- Other treatment options include: immunosuppressive agents (cyclosporine and cyclophosphamide), Plasmapharesis.

Early blister stage of TEN

# Venous ulceration

Venous ulceration is typically **seen above the medial malleolus.**

**The incidence of venous leg ulceration is higher in:**

- obese patients
- history of varicose veins
- **history of deep vein thrombosis**

**Ulcers occur owing to:**

- venous stasis
- secondary increase in capillary pressure
- fibrosis
- poorly nourished skin particularly over areas such as the medial malleolus

## Investigations:

- **Ankle-brachial pressure index (ABPI)** is important in **non-healing ulcers** to assess for poor arterial flow which could impair healing.
- An ankle-brachial pressure index measurement would help exclude arterial insufficiency as a contributing factor. If this was abnormal then a referral to the vascular surgeons should be considered.
- The ABPI readings indicate a reasonable arterial supply and suggest the ulcers are **venous in nature**.
- A **'normal' ABPI** may be regarded **as between 0.9 - 1.2**.
- **Values below 0.9 indicate arterial disease**.
- Interestingly, **values above 1.3 may also indicate arterial disease**, in the form of **false-negative results secondary to arterial calcification** (e.g. in **diabetics**).

## Management:

- **Compression multi-layer bandaging**, usually 4 layer: it is the **only treatment shown to be of real benefit**, it reduce LL oedema and improve the chances of healing.
- It is also crucial for patients to rest and keep the leg up where possible.
- Oral pentoxifylline, a peripheral vasodilator, improves healing rate.
- Small evidence base supporting use of flavonoids
- Little evidence to suggest benefit from hydrocolloid dressings, topical growth factors, ultrasound therapy and intermittent pneumatic compression.
- If the ulcer fails to heal with active management (e.g. Compression bandaging) then referral for consideration of biopsy to exclude a malignancy should be made.

**Management of venous ulceration > compression multi-layer bandaging**

**ABPI** measurement is essential before beginning bandaging, as if there is significant arterial insufficiency, blood supply to the limb may be threatened. An ABPI of **0.8** has become a **pivotal figure** in the management of leg ulceration, defining the **cut-off point** for high compression banding and is frequently taken as indicating the presence of a so-called "**mixed ulcer**".

## Vitiligo

Vitiligo is an **autoimmune** condition which results in the loss of melanocytes and consequent depigmentation of the skin.
It is thought to affect around **1%** of the population and symptoms typically develop by the age of **20-30 years**.

### Features:

- **Well demarcated patches** of **depigmented skin.**
- The peripheries tend to be most affected.
- **Trauma may precipitate new lesions (Koebner phenomenon).**

### Associated conditions:

- **Pernicious anaemia (in 9%)**
- **Type 1 DM (in 5.7%)**
- **Autoimmune thyroid disorders** (as Hashimoto thyroiditis & Graves')
- **Addison's disease**
- **Polyglandular autoimmune syndrome**
- **Alopecia areata**

- **Rheumatoid arthritis,**
- **Inflammatory bowel disease**
- **Psoriasis.**

**NB: HLA-B13** appears to be the link between thyroid disease and vitiligo.
**NB**: 9% of patients with pernicious anaemia have been shown to have vitiligo, compared to 5.7% with DM.

### Management:

- Sun block for affected areas of skin.
- Camouflage make-up.
- Topical corticosteroids may reverse the changes if applied early.
- There may also be a role for topical Tacrolimus and phototherapy, although caution needs to be exercised with light-skinned patients.

## Zinc deficiency

### Features:

- **Perioral dermatitis**: red, crusted lesions
- Acrodermatitis
- **Alopecia**
- **Short stature (Dwarfism)**
- Hypogonadism
- **Hepatosplenomegaly**
- **Geophagia** (ingesting clay/soil)
- Cognitive impairment (mental lethargy)

**NB**: Zn deficiency is associated with **adverse pregnancy outcomes**.

**NB:** Zn supplementation has also been shown to improve neuropsychological function in Chinese children.

**EX:** A 25-year-old female presents with **red crusted** lesions **around the mouth** and **finger pulps** three months after having had **small bowel resection** for **Crohn's** disease.
What is the most likely cause of her skin condition >> **Zinc deficiency.**

## Yellow nail syndrome

Slowing of the nail growth leads to the characteristic thickened and discoloured nails seen in yellow nail syndrome.

### Associations:

- **Congenital lymphoedema**
- **Pleural effusions**
- **Bronchiectasis**
- **Chronic sinus infections**

"وما توفيقى الا بالله "

# Referances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